Role of Diffusion Weighted Imaging (DWI) in determining response to neoadjuvant chemoradiation in locally advanced carcinoma rectum

A dissertation submitted in partial fulfillment of MD Radiodiagnosis (Branch VIII) examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014

CERTIFICATE

This is to certify that the dissertation entitled "Role of Diffusion Weighted Imaging (DWI) in determining response to neoadjuvant chemoradiation in locally advanced carcinoma rectum" is the bonafide original work of Dr.Kirthi Sathyakumar submitted in partial fulfilment of the requirement for MD Radiodiagnosis (Branch VIII) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2014.

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INTRODUCTION The treatment of locally advanced rectal cancer involves pre-operative chemoradiotherapy (CRT) followed by surgery after an interval of approximately 6 weeks. The response to CRT is assessed using the histopathological tumour regression grade (TRG), following surgery. High resolution T2W MRI is excellent in determining the extent of the tumour. It is also used in reassessing the tumour after pre-operative CRT. Tumour regression and downstaging is an important prognostic factor in local tumour recurrence rate and 5- year survival. However, when it comes to re-staging after CRT there is difficulty in recognizing residual tumour in areas of radiation induced fibrosis, desmoplasia...

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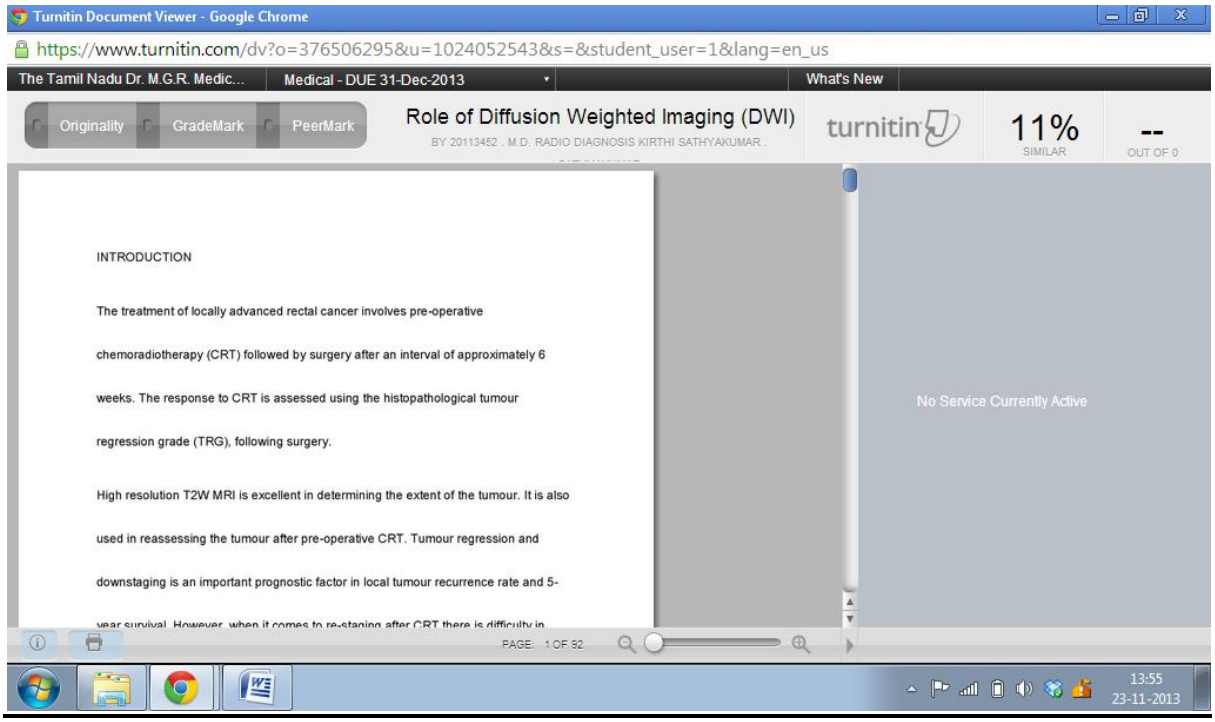

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January 13, 2012

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Sub: **FLUID Research grant project NEW PROPOSAL:**
Evaluation of response to neoadjuvant chemoradiation in patients with locally advanced carcinoma rectum using Diffusion Weighted Imaging
Dr. Kirthi Sathyakumar, Radio diagnosis, Dr. Anu Eapen, Dr. Anuradha, Radio Diagnosis, Dr. Mark Ranjan Jesudason, Surgery, Dr. Anna Pulimood, Dr. Dipti Masih, Pathology.

Ref: IRB Min. No. 7657 dated 18.11.2011

Dear Dr. Sathyakumar,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Evaluation of response to neoadjuvant chemoradiation in patients with locally advanced carcinoma rectum using Diffusion Weighted Imaging" on November 18, 2011.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Information Sheet and Informed Consent Form (English, Tamil and Hindi)
3. Proforma
4. Cvs of Drs. Kirthi Sathyakumar, Anu Eapen, Anuradha, Anna Pulimood
5. A CD containing document 1 – 4

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on November 18, 2011 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

A sum of ₹ 79,000/- (Rupees Seventy nine thousand only) is sanctioned for 2 years.

Yours sincerely,

Alfred Daniel

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
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Above all I thank, God for his abundant grace.

CONTENTS

INTRODUCTION

The treatment of locally advanced rectal cancer involves pre-operative chemoradiotherapy (CRT) followed by surgery after an interval of approximately 6 weeks. The response to CRT is assessed using the histopathological tumour regression grade (TRG), following surgery.

High resolution T2W MRI is excellent in determining the extent of the tumour. It is also used in reassessing the tumour after pre-operative CRT. Tumour regression and downstaging is an important prognostic factor in local tumour recurrence rate and 5-year survival. However, when it comes to re-staging after CRT there is difficulty in recognizing residual tumour in areas of radiation induced fibrosis, desmoplasia and mucinous change.

Prediction of tumour response before onset of treatment could have considerable clinical benefit, especially in prognostication and tailoring of therapy.

Because of its promise in cancer imaging, we have looked at the potential role of DWI in carcinoma rectum. The hypothesis is that DWI can be more valuable than standard T2W MRI in recognizing viable tumour remnants in areas of radiation induced fibrosis.

For this purpose, quantitative assessment by means of volumetric measurements and apparent diffusion co-efficient (ADC) measurements were looked at, and the performance of DWI was compared with standard T2- weighted MR images, using the histopathological tumour regression grade as the gold standard.

Secondly, there is recent interest in assessing tumour regression grade on MRI. Hence, the performance of TRG assessed using T2W MRI and DWI was also correlated with the histopathological TRG.

AIM

To assess the role of Diffusion Weighted Imaging in prediction of response to neoadjuvant chemoradiation in patients with locally advanced carcinoma rectum

OBJECTIVES

a) To identify the role of different parameters in diffusion weighted imaging in predicting response to neoadjuvant chemoradiation in patients with locally advanced carcinoma rectum, in comparison with histopathological tumour regression grade. The variables studied will include

- Tumour volume pre- chemoradiation, using DWI Volumetry

- Tumour volume post- chemoradiation, using DWI Volumetry

- Percentage reduction in tumour volume following chemoradiation (TVRR)

- ADC value of tumour pre- chemoradiation

- ADC value of tumour post- chemoradiation

- Change in the ADC value (ΔADC) and tumour ADC increase rate (TAIR)

b) To compare the performance of DWI with that of conventional T2W MRI in the prediction of response to chemoradiation.

c) To study the comparability between MR tumour regression grade separately assessed with T2W HR and DWI with histopathological tumour regression grade

REVIEW OF LITERATURE

CARCINOMA RECTUM AND NORMAL RECTAL ANATOMY

The rectum is a long tubular organ extending from the restosigmoid junction to the anal canal. It measures approximately 15 cm in length. The rectum can be divided into three segments for describing the location of the lesions. The lower one-third corresponds to the first 7-10cm from the anal verge, the next 4-5cm constitutes the mid-third and the last 4-5cm forms the upper –third of the rectum.(2)

The lower limit of the rectum is formed by the levator ani muscle/puborectalis sling where it inserts into the rectal muscular layer. The rectum is surround By fatty tissue termed as the mesorectum which contains lymph nodes, vessels and fibrous septae. The mesorectal fascia forms a thin covering over the mesorectum.

The rectal wall is made up of three different layers – the mucosa, submucosa and muscularis propria followed by a serosal covering.

THE GLOBAL SCENARIO

Rectal cancer is one the most common cancers of the GI tract, having a high disease related mortality. The incidence of rectal cancer is more than that of the other colonic cancers. Among the colorectal cancers, one third occur in the rectum(3). Colorectal cancers account

for around 400,000 deaths per year worldwide. Of the 5.2 million deaths/year due to various cancers, 55% occur in developing countries.(4)

THE INDIAN SCENARIO

The incidence of rectal cancer in India is 4-5/lakh population (4). Despite the low incidence, absolute number of cases in India is high due to the large population. Due to delay in diagnosis and referral from peripheral parts of the country, majority of the cases present in a locally advanced stage.(6)

There is a slight male predilection and increase in incidence beyond 50 years of age. The other observation that has been made is the increasing occurrence in young adults. This was particularly evident in the Indian series where the number of young patients was relatively higher. The incidence rates in urban individuals is observed to be higher and is almost twice that of the rural incidence rates.(7)(8)

There are various risk factors known to be associated with rectal carcinomas. Among these are; adenomas, dietary and environmental factors, inflammatory bowel disease.(9) The adverse factors incriminated being obesity, physical inactivity, consumption of red meat and genetic susceptibility. On the other hand, dietary fibres, fruits, polyunsaturated fatty acids from fish and phytochemicals are probably protective.(9,10)

Histologically, adenocarcinoma accounts for most of the cases (98%). The other types encountered are rectal carcinoid (0.1 %), lymphoma (1.3 %), GIST (<1%) and an occasional melanoma.(2)

The mortality rate from rectal cancer over the past decade has significantly reduced when compared to the statistics before 1995. This has been shown to be due to the neoadjuvant therapy and a novel surgical technique called total mesorectal excision (TME)(3,11).

Downstaging of tumour with neoadjuvant concurrent chemoradiotherapy , followed by surgery has significantly reduced tumour recurrence rate and improved disease free survival in patients with carcinoma rectum.(11)

The current indications for neoadjuvant chemo-radiotherapy are locally advanced rectal cancers (T3,T4 disease), tumours close to the mesorectal fascia(<3mm) and nodal involvement. Post-operative adjuvant radio/chemotherapy is given if the CRM on histopathology is <2mm and for perforation of tumour during the operative procedure. Concomitant chemotherapy and radiotherapy is given over 25 days in 2Gy fractions.(13)

A complete pathological response with no evidence of residual tumour may be seen in as many as 38% of patients (13). However it has been noticed that there is a significant individual variation of response to preoperative CRT; 9%-25% of patients show complete response, 54%-75% show tumour downstaging and the others would show no response. Hence, early assessment of response would be highly beneficial, so that treatment can be intensified for those patients who may not show a response.(14)

Traditional surgery consisted of resection of tumour with a margin of surrounding peri-rectal fat. This method had a high recurrence rate of around 40%.The present surgical treatment for locally advanced disease is total mesorectal excision (TME) wherein the entire rectum and mesorectal fat is excised by dissecting along the mesorectal fascia.

TME has shown to improve disease free survival and reduce recurrence rate when compared to conventional surgery (11% vs 40% previously).(15)

This is now the preferred method for locally advanced tumours, the choice of low anterior resection or abdominoperineal excision being made depending on the location of the tumour. High and mid rectal growths can be excised using a low anterior resection whereas low rectal carcinomas require abdomino-perineal excision followed by a colostomy

In early cancers (stage T1 and T2) which are confined to the mucosa and submucosa, primary surgery or transanal endoscopic microsurgery with full thickness excision of the tumour are the options of treatment.

Recently, Habr-Gama et al treated patients with a complete clinical response with observation alone (wait and see approach). Compared with the patients who underwent surgery after tumour regression, the five-year survival rates and disease free survival were better in this subgroup(17).

Though the trend is towards conservative approach in many countries, this recent form of treatment is still controversial. The adoption of this approach, makes preoperative assessment of tumour regression and identification of complete response very important.

IMAGING IN CARCINOMA RECTUM

The primary aim while staging rectal cancer preoperatively is to categorize the patients based on the risk of recurrence by accurate staging. This has significant clinical implication in terms of treatment planning

Staging should be able to identify(2)

1) Those patients with extramural disease who will require neoadjuvant chemoradiation (locally advanced –T3,T4)

2) Those patients with no involvement of the anal sphincter/levator ani who will benefit from a sphincter sparing surgery

The diagnosis and staging of rectal cancer is largely done using MR imaging worldwide. MRI shows greater soft tissue resolution with ability to image in multiple planes. There is also no additional risk due to radiation. The high resolution images are particularly useful in accurate depiction of rectal anatomy(18).

T2 weighted high resolution images are commonly used to study the different layers of the rectal wall. Three such layers can be distinguished – an inner hyperintense layer representing mucosa and submucosa, a middle hypointense layer representing the muscularis externa and an outer hyperintense layer depicting the perirectal/mesorectal fat. External to this, the mesorectal fascia forms a thin hypointense covering to the mesorectal fat(2). The

mesorectum gradually tapers and merges with the rectal wall at the anorectal junction. There is no serosal covering over the rectum.

The tumoral tissue usually has an intermediate signal intensity and T2 weighted images are used to stage the tumour according to the TNM staging. The tumour can be polypoid, plaque like or circumferential(18).

MR IMAGING INTERPRETATION

Interpretation of pelvic MR images is prone to considerable interobserver variability and requires a thorough knowledge of the disease process, the parameters determining disease severity and the implications of false positive / negative findings(18).

Recently, Brown et al proposed a way to standardise reporting and at the same time provide a systematic approach to include all the necessary information. The pneumonic 'DISTANCE' was used for this purpose(19).

(a) Distance of the tumour from the anal verge (DIS) (19)

Rectal cancers are divided into upper, mid and low rectal malignancies based on the distance measured from the lower end of the tumour to the anal verge. The surgical technique and also the outcome is dependent on the location of the tumour

- Upper rectal cancers: The inferior edge of the tumour is more than 10cm from the anal verge. This is of importance because the peritoneal reflection lies over the anterior wall of the upper rectum. There is hence a risk of involvement by tumour and injury during surgery.

- Mid rectal cancers: The inferior edge of the tumour lies between 5-10cm from the anal verge. Tumours in this site have a more favourable outcome, as the entire segment is covered by mesorectum and is away from the peritoneal reflection.
- Low rectal cancers: The inferior edge of the tumour lies less than 5cm from the anal verge. The mesorectum tapers at this level, therefore the risk of involvement of the mesorectal fascia is higher. The upper end of the puborectalis muscle is seen at the level of the anorectal junction. The low rectal tumours also pose a risk of involvement of the internal and external sphincters.

(b) T- Staging of rectal cancer

The T-stage of the tumour indicates the depth of invasion

- **Stage T1** tumours involves the mucosa and submucosa and spares the muscular layer of the rectal wall.
- **Stage T2** tumours are characterised by infiltration of the muscular layer. The outer border between the muscularis and the mesorectal fat is intact and can be visualised as a thin hypointense line.
- **Stage T3** tumours extend beyond the rectal wall and infiltrate the mesorectal fat. On imaging, this is identified by the inability to visualise the interface between the muscularis and the perirectal fat. The recent American Joint Committee on Cancer 2010, sub classifies T3 in three subgroups. This is because various studies have shown that the depth of extramural spread is an important prognostic factor(20,21).
    - T3a – Tumour extends <1mm beyond the muscularis propria
    - T3b - Tumour extends >1-5 mm beyond the muscularis propria

    - T3c - Tumour extends > 5-15 mm beyond the muscularis propria
    - T3d - Tumour extends >15 mm beyond the muscularis propria
- **Stage T4** tumours infiltrate the surrounding organs and muscles of the pelvic wall
    - T4a – Tumour penetrates visceral peritoneal surface
    - T4b – Tumour invades other organs or structures

Differentiating T1 from T2 tumours can be difficult on conventional MRI. However, the higher grade tumours where there is infiltration of the mesorectal fat can be accurately differentiated.

The accuracy of MRI in T-staging ranges from 59-95%(22–24).

(c) A – Assessment of anal complex (Internal/Extenal sphincter and Puborectal muscles)

This is mainly for low rectal cancers which are associated with higher recurrence rates and increased morbidity(26). These tumours are treated by abdominoperineal excision and a permanent stoma.

Neoadjuvant CRT in many of these tumours can lead to significant disease regression and preservation of sphincters. Such tumours can even be treated with a sphincter sparing surgery followed by coloanal anastomosis(26,27).

T2W HR coronal images are most accurate for assessment of the anal complex. Sphincter involvement can be excluded if the lower end of the tumour lies above the puborectalis sling.

For tumours that extend below this point, the involvement of the muscularis propria (internal sphincter), intersphincteric plane and external sphincter should be carefully assessed (19).

(d) N- Staging of rectal cancer

When it comes to N staging there is considerable variability and a clear consensus has not yet been established. MRI has low sensitivity and specificity for the detection of nodal metastases with accuracy ranging from 43-85%. This is due to the fact that small lymph nodes still have a high prevalence of malignancy – 9% in 1-2mm nodes and 17% in 2-5mm nodes.

The various parameters used in nodal staging are the size , morphology and signal intensity. Studies have shown that detection based on shape, border and signal intensity is more reliable than size criteria alone because more than 50% of the nodes are <5mm in diameter(28,29). Some consider any detectable node as possibly malignant while some authors have also provided a size criteria (larger than 5mm / 10mm)(28). The morphological parameters considered to be in favour of malignancy are the presence of indistinct or spiculated nodal margins and a mottled heterogeneous appearance (29,30). The use of RES specific ultra-small iron based particles (USPIO) has also proven to be helpful. These particles are not taken up by the neoplastic cells replacing the lymph nodes and hence the pathological nodes can be differentiated. The involved nodes will not demonstrate the signal drop produced by the paramagnetic effect of USPIO particles. The use of these particles has a higher specificity of ~75%, however the sensitivity is the same as morphological parameters(30).

N-STAGING: AJCC 2010 7th edition

	N0	**No regional lymph nodes**
	N1	Metastasis to 1-3 regional lymph nodes
N1a		Metastasis to 1 regional lymph node
N1b		Metastasis to 2-3 regional lymph nodes
N1c		Tumour deposits in the subserosa, nonperitonealized perirectal tissues or mesentery without regional nodal metastasis
	N2	Metastasis to 4 or more regional lymph nodes
N2a		Metastasis to 4-6 regional lymph nodes
N2b		Metastasis to 7 or more regional lymph nodes

Table.1: Nodal staging of rectal cancer adapted from AJCC 7th edition

(e) C – Circumferential resection margin (CRM)

The other important parameter that needs to be assessed is the circumferential resection margin (CRM). This refers to the minimum distance between the tumour and the mesorectal fascia at any point along its entire extent. This is the most important parameter is predicting disease free survival and recurrence after surgical excision (2,32,33). This parameter becomes important especially in T3 tumours aiding in risk stratification and treatment planning.

A positive CRM is defined as tumour lying within 1mm of the mesorectal fascia.

MRI has been proven to be highly accurate in assessing the CRM and thereby the involvement of the mesorectal fascia. According to a study, done by Bees-Tan and others(22) - a CRM of 5mm on MRI can predict tumour- mesorectal fascia distance of atleast 1mm on histopathology with a high degree of confidence (of around 97%)

Hence, the local recurrence is dependent on the CRM and involvement of mesorectal fascia; ie a short tumour –mesorectal fascia distance is the most important parameter predicting disease free survival. The T-staging system does not actually differentiate between the T3 tumours which have a wide CRM and those with a narrow CRM. Both will be classified under the same stage. It is therefore of importance to accurately assess the CRM in addition to the TNM stage.

There are four different patterns in which the CRM can be involved (20)

A – By suspicious lymph nodes
B – By the main tumour itself
C – By extramural vascular invasion
D – By a tumour deposit in the mesorectum

Table.2: Patterns by which CRM can be involved in locally advanced rectal cancer

(f) E – Extramural vascular invasion

Extramural vascular invasion (EMVI) is another important prognostic factor which can predict disease free survival, local and distant recurrence(34). it can be seen in 50% of the patients (20). High resolution MRI has been shown to help in identifying this parameter which was otherwise only available from the post operative surgical specimen(34).

EMVI is identified by the presence of tumour cells within the blood vessels located in the mesorectal fat. Features that would suggest EMVI are (20)

- Presence of tumour signal within a mesorectal vessel
- Expansion of the vessel
- Extension of tumour through the vessel wall with disruption of its borders

(g) M - Staging of rectal cancer

Distant metastasis is classified as follows – AJCC 2010

M0	**No evidence of distant metastasis**
M1	Distant metastasis is present
M1a	Metastasis to one organ or site (ex liver/lung/non regional node)
M1b	Metastasis to more than one organ/site or peritoneum

Table.3: M- staging of rectal cancer adapted from AJCC 7th edition

PATHOLOGICAL ASSESSMENT OF TUMOUR REGRESSION AFTER PREOPERATIVE CHEMORADIOTHERAPY

Following neoadjuvant chemoradiotherapy the most important pathologically determined prognostic factors are CRM, ypT & ypN (T and N stage of the resected specimen) and the histological tumour regression grade (36).

It has been shown that the visual assessment of the degree of fibrosis in the pathological specimen can be used to categorize tumour regression into grades. This is considered to be an important predictor of overall survival and disease free survival (36,37).

The histopathological features of regression were first studied by Mandard et al for esophageal carcinoma. The disease regression was quantitatively assessed and a grading system was proposed(38).

The surgical specimens were analysed and the cases were divided into two groups – the first group did not show any regressive changes. The second group included all cases which showed features of regression. These changes were as follows: -Cytoplasmic vacuolation, nuclear pyknosis and necrosis within the cancer cells- Stromal fibrosis with or without inflammatory infiltration.

Based on these findings, tumour regression was classified into 5 tumour regression grades

TUMOUR REGRESSION GRADE	CRITERION
GRADE 1 (Complete regression)	Absence of residual cancer and fibrosis extending through the wall
GRADE 2	Rare residual tumour cells scattered throughout the fibrosis
GRADE 3	Predominant fibrosis but increase in the number of cancer cells
GRADE 4	Residual cancer cells outgrowing the fibrosis
GRADE 5	Absence of regressive changes

Table.4: Mandard's tumour regression grading system(TRG)

Their results showed that the tumour regression grades correlated with disease free survival ($p < 0.05$)

The tumour regression grades could be further grouped into two which was clinically relevant (TRG 1-3 vs TRG 4-5) and were a significant predictor of patient survival ($p < 0.001$)

In this study, the authors also described that the tumour regression paralleled regression of lymph node metastases.

A pathological complete response (pCR) has the most favourable outcome with regard to both survival and recurrence (39).

The TRG has been consistently shown to be an independent prognostic factor which can predict long-term outcome following pre-operative chemo/radiotherapy in rectal cancer in subsequent studies as well.

Some authors also quote the Dworak tumour response grading system(37).

Grade 0 - No response

Grade 1 - Dominant tumour mass with obvious fibrosis and vasculopathy (minimal response)

Grade 2 - Dominant fibrosis with a few easily identifiable tumour cells or groups (moderate response)

Grade 3 - Fibrotic tissue with a few difficult to find tumour cells with or without mucous material (near complete response)

Grade 4 - No viable tumour cells (complete response)

Braun et al, performed a similar regression grading system for head and neck tumours. They also reported a significant correlation between tumour regression grades and patient survival (40).

Hence tumour regression grading of tumours is useful in prognostication and there is correlation between response to neoadjuvant therapy and patient survival.

RE-STAGING ON MRI FOR LOCALLY ADVANCED CARCINOMA RECTUM (41–43)

Patients with locally advanced rectal cancer in whom there is invasion of the mesorectal fat and when the CRM, sphincteric involvement is threatened, undergo neo-adjuvant chemo-radiotherapy for downstaging the disease (ideally T3 disease and beyond).

Pathologically the tumour regression has been traditionally classified as complete response (no residual tumour), partial response (downstaging of >50%) and no response, which was done after the surgery. Of late, pre-operative assessment of tumour downstaging is being routinely performed using high resolution T2-weigted MRI.

The accuracy of routine T2W HR MRI in predicting tumour stage and response is as follows(43)

	NON IRRADIATED RECTAL CANCER	AFTER IRRADIATION
T STAGE	85%	50%
N STAGE	75%	65%
CRM	92-95%	66%

Table.5: Accuracy of T2W MRI in predicting stage of rectal cancer pre and post-CRT

* mean values

The morphological changes seen after radiotherapy include fibrosis, demoplastic response, mucinous change and inflammation.

These changes can be appreciated on MRI (43).

- **Areas of fibrosis** appear as very low signal intensity compared to the intermediate signal intensity seen in residual tumour.

- **Desmoplasia or reactive fibrosis** is due to stromal collagen deposition and does not contain tumour cells. This is seen as low intensity strands radiating from the tumour edge.

- **Mucinous change or colloid response** appears as very high signal intensity areas (20, 43). This can be interpreted in three different ways.

- Firstly, non mucinous tumours showing areas of mucinous change on post- CRT scans indicate areas of necrosis and cystic transformation.
- Secondly, mucinous rectal tumours can demonstrate residual mucin components with no or minimal intermediate signal areas within. This represents acellular mucin and does not contain viable tumour within.
- In the third scenario, there are the mucinous tumous showing non-response. These tumours are of high signal intensity with intermediate signal components which are unchanged from the baseline.

During evaluation for re-staging, the same parameters and diagnostic clues described previously (goes by the pneumonic DISTANCE) are used (20). Both the pre and post – CCRT images should be looked at and compared for changes in tumour bulk, extent and signal intensity. The T-staging categories are same as those used in the baseline assessment

The CRM is also again assessed. The CRM is considered to be infiltrated if the minimum distance between the tumoral edge and the mesorectal fascia is less than or equal to 1mm. The accuracy of MRI in this regard is however low, because it is difficult to differentiate a fibrotic scar adjacent to the mesorectal fascia from viable tumour (20).

The mesorectal and perivascular lymph nodes are assessed with criteria similar to that in the pre-CCRT MRI.

The other important parameters to be identified are invasion of puborectalis muscle, anal sphincter, prostate/seminal vesicles and uterus/vagina.

The majority of imaging assessment is done on T2W high resolution scans

After the MERCURY (Magnetic Resonance Imaging in Rectal Cancer European Equivalence Study) trial, a tumour regression grading system on MRI was proposed (4). This again has shown to be a strong indication of tumour recurrence and final outcome of disease.

The grading system reflected the histopathological method of tumour regression grading. In this, the tumour is assessed for the presence of fibrous signal intensity (markedly hypointense) and tumour signal intensity.

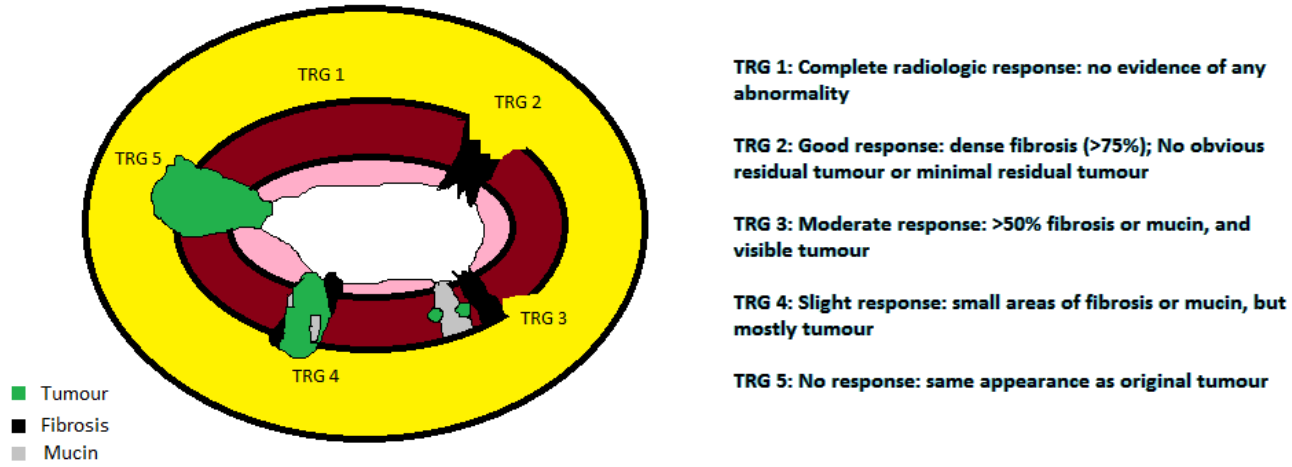
The high resolution images are compared with the baseline scan .

The authors concluded that assessment of TRG and CRM on MRI are important markers predicting survival outcome.

TUMOUR REGRESSION GRADE	CRITERION
1	Predominant fibrosis with no residual tumour
2	Predominant fibrosis with minimal residual tumour signal
3	Predominant fibrosis with substantial residual tumour signal
4	Predominant tumour signal fibrosis with minimal fibrosis
5	Tumour unchanged from baseline

Table.6: MR tumour regression grading system

SCHEMATIC REPRESENTATION



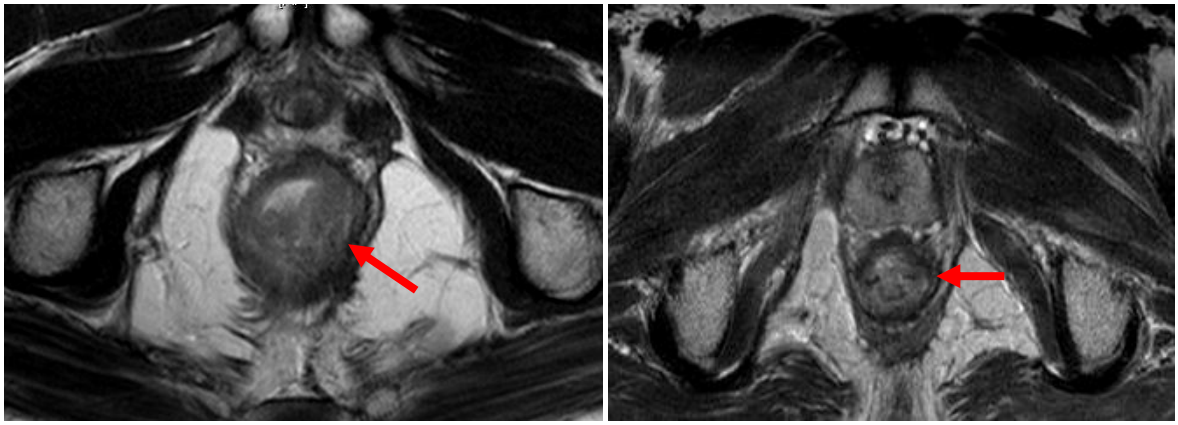


Fig.1a

TRG 1 – No residual tumour signal

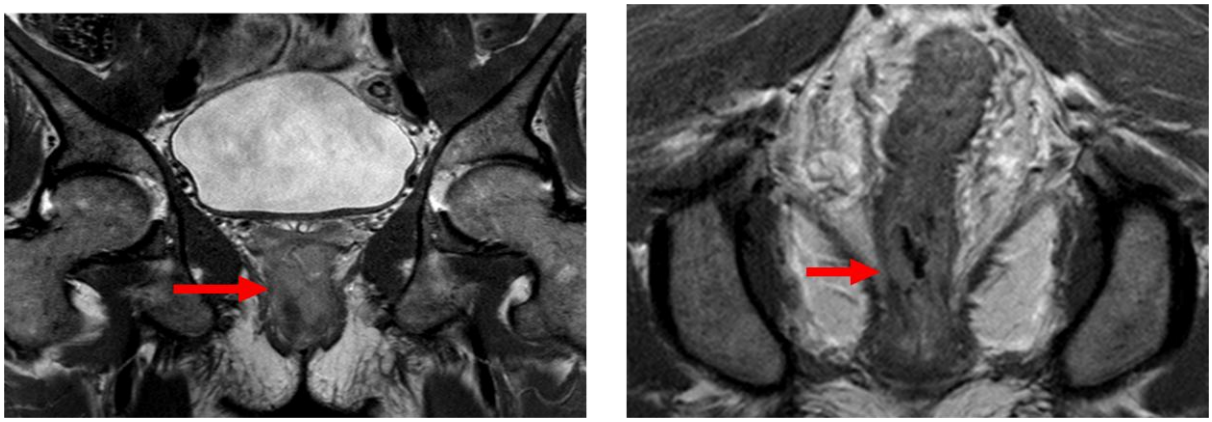


Fig.1b Pre CRT Post CRT

TRG 2 – Scanty residual tumour signal

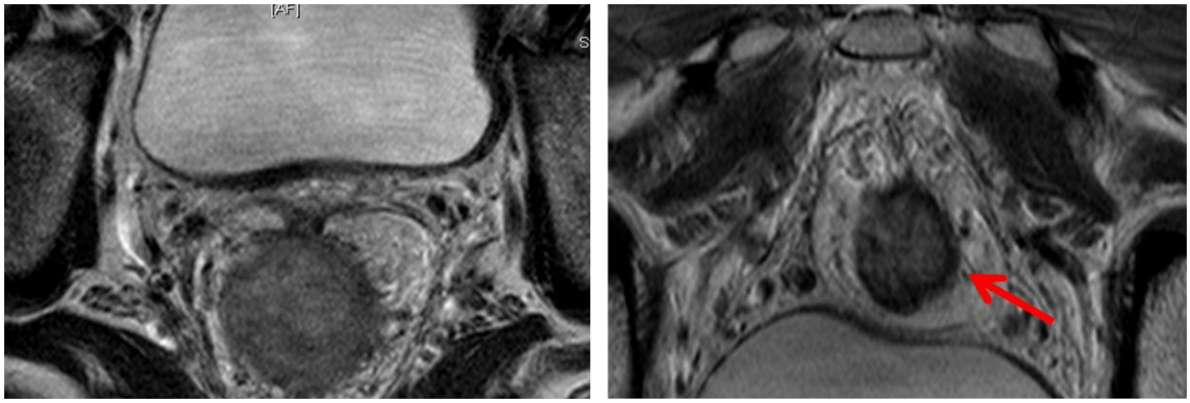


Fig. 1c Pre CRT Post CRT

TRG 3 – Residual tumour not exceeding fibrosis

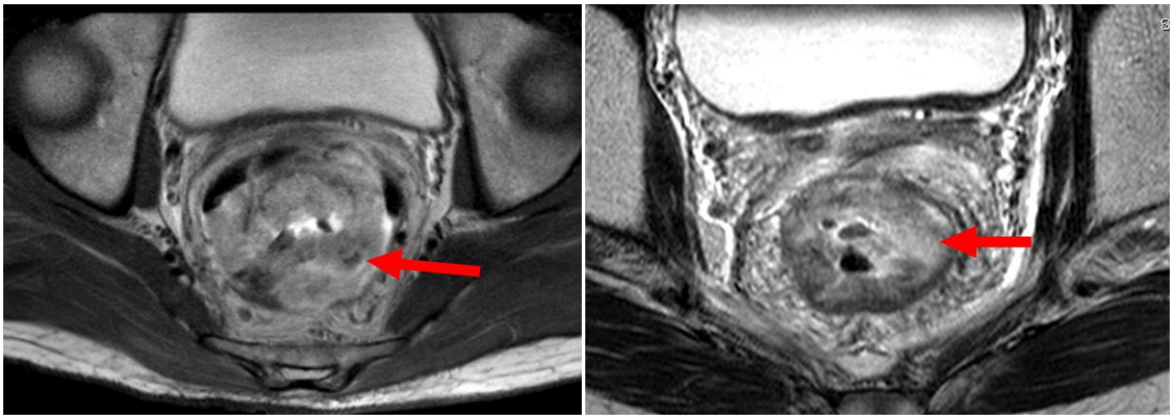


Fig.1d Pre CRT Post CRT

TRG 4 – Tumour with minimal fibrosis

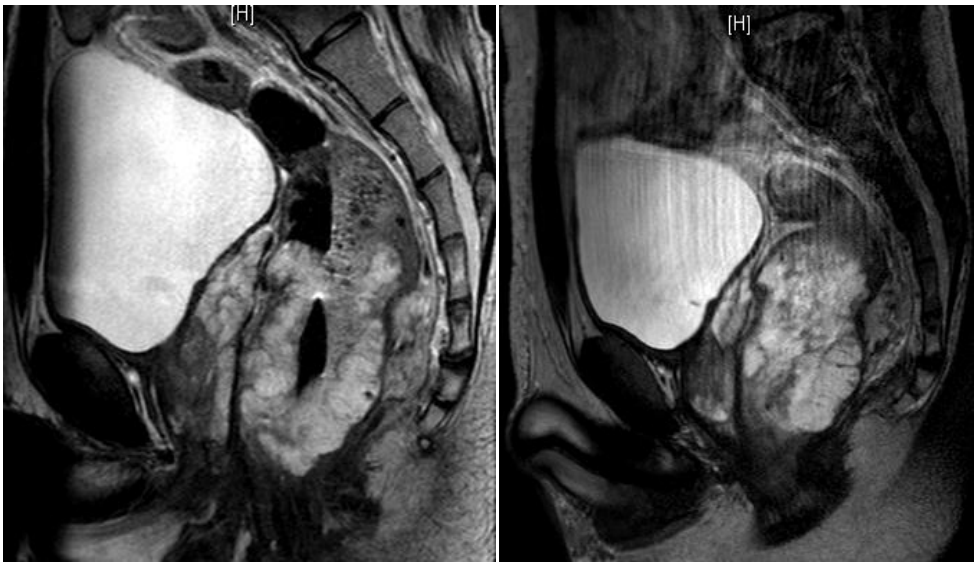


Fig. 1e

TRG 5 – Tumour unchanged from baseline

Fig.1(a-e): Tumour regression grade based on MRI T2w imaging. The first image corresponds to the pre-CRT MRI while the second image shows the post CRT MRI. a-e depict grades 1-5 respectively

However re-staging in an irradiated rectum is prone for error and there are many examples quoted in literature for both overstaging and understaging.

Overstaging is mainly due to the presence of hypointense soft tissue in the region of the tumour. This can be related to fibrosis or desmoplastic reaction due to peritumoral infiltration by inflammatory cells. The presence of radiation proctitis and related ulceration also leads to misinterpretation as residual disease. T1 and T2 disease is mainly prone for overstaging (43,20).

Understaging is due to the difficulty in visualising small residual tumour in a background of fibrosis and radiation related changes in the rectal mucosa.

In conclusion, the parameters are to be assessed while restaging rectal cancer are (42)

1. Appearance of the tumour, presence of necrotic and mucinous components 2. Distance from the anal verge
3. Length of the residual tumor compared to the baseline and depth of extramural spread
4. MRI tumour regression grade
5. MRI TNM stage
6. The circumferential resection margin (CRM)
7. Involvement of the peritoneal reflection

RECENT ADVANCES AND METHODS USED IN RE-STAGING RECTAL CANCER ON MRI

Recently, **MR Volumetry, diffusion and perfusion weighted imaging** have been looked at for improving diagnostic accuracy in assessing residual disease.

Dynamic contrast enhanced T1W perfusion studies have been analysed to predict tumour behaviour. Increased perfusion within a tumour represents increased microcirculation. This is said to reflect angiogenic activity and arterovenous shunting within the tumour, findings suggestive of an aggressive tumour (44,45).

MR VOLUMETRY

MR volumetry performed on T2W high resolution scans has shown to correlate well with the histopathological estimation (46).

Many studies have looked at the tumour volume reduction rate (TVRR), calculated as a percentage by comparing the pre and post CRT studies. The calculation of volume can be done either as a semi automated process or by manually tracing the tumour on all sections. A three dimension region of interest volumetry has also shown promise in estimating volumes (47).

A regression of the tumour volume by more than 70% is said to be associated with a lesser risk of recurrence, better outcome and good tumour regression on histology, with TVRR being an independent prognostic parameter(48).

A tumour volume reduction of >75% has shown to have a significant association with pathological complete response (ypT0 or TRG 1) (49).

Another study by Yeo et al showed that a TVRR significantly correlated with histopathological downstaging of the tumour and tumour regression grade. They proposed a cut off of >60% for good regression, downstaging and ypT1-2, ypN0 rates. A TVRR of >80% was associated with complete regression (46) .

MR volumetric studies performed on T2W HR images are quite reproducible even by non specialist radiologists. This has shown benefit especially in low rectal growths where assessment of the CRM and T-stage is difficult (48).

However, morphologic assessment of post CRT T2W images is difficult due to the presence of fibrosis and the inability to accurately determine if there is residual tumour in these regions of fibrosis. Also it is often difficult to appreciate scanty intermediate signal due to residual disease in areas of extensive fibrosis. (20)

In view of these disadvantages, MR volumetry frequently over-estimates the tumour volume.

DIFFUSION WEIGHTED IMAGING (DWI)

Image contrast is provided in diffusion weighted images by utilising the property of random motion of water molecules within various tissues (also known as Brownian motion). In this technique, diffusion sensitising gradients are applied around a 180 degree refocusing

radiofrequency pulse of a T2 weighted sequence. The corresponding signal loss is measured and represented on the Diffusion Weighted images (50).

The acquisition of diffusion weighted images (DWI) also depends on the strength of the diffusion sensitising gradient or diffusion coefficient which is expressed by the b-value. Characteristic B values used in pelvic MRI are 0 and 1000 (51).

Using this technique the tissues with relatively stationary water molecules (ie there is restriction of diffusion of particles) appear brighter than those tissues where there is free molecular movement. Visual inspection of the diffusion weighted images is used in the assessment of diffusion properties of tissues.

In addition to diffusion contrast, diffusion images also have an overlying T2 contrast. In regions of long T2 this simulates diffusion restriction (T2 shine through effect). This can be eliminated by calculating the pure diffusion coefficient.

The diffusion coefficient is a measure of the strength of diffusion restriction.

DWI can determine the diffusion coefficient in each voxel. This is called the apparent diffusion coefficient (ADC). **The ADC map is a pixel-by-pixel display of all diffusion coefficients.**

Quantitative analysis can be performed using the ADC maps (apparent diffusion coefficient). This is obtained by post processing of the DWI with atleast two different b values (monoexponential decay model). In the ADC map, diffusion restricted areas appear dark

corresponding to the bright areas on DWI. ROIs (region of interest) are drawn on the ADC map to obtain the ADC value (50).

The ADC map has a combined effect of the water diffusion and capillary perfusion in the extracelluar space. The effect of perfusion is most pronounced at low b-values (5-100 sec/mm2). On the other hand, high b-values (ex 1000 sec/mm2) overcome this effect and hence more effectively depict the cellularity of the lesion (52).

Role of DWI in oncology

Diffusion weighted imaging (DWI) improves tumour detection when used in conjunction with standard T2W MRI. Since DWI is an indicator of cellularity of a lesion , quantitative assessment by using ADC values can be used to predict residual tumour, necrotic areas and thereby the tumour aggressiveness (14).

Many studies have investigated the use of diffusion weighted imaging in prostate , liver, renal and breast imaging (51). There are few studies which have looked at its utility in evaluating rectal cancer, more specifically its utility in tumour downstaging (53–59).

Role of DWI in rectal cancer imaging (Re-staging after preoperative chemoradiation)

It has become important to assess tumour downstaging after preoperative chemo-radiation as this depicts the local recurrence and 5 year survival rate (60). A few studies have tried to utilize DWI in this respect.

It has been postulated that DWI can be used for diagnosis of early radiation induced fibrosis and hence prevent overstaging of disease. Delineation of residual tumour might be better appreciated on DWI than conventional T2W images (20, 54).

The initial studies on DWI used only visual analysis in conjunction with T2W MR. They did not incorporate quantitative assessment criteria. Authors have shown good result on using DWI in conjunction with standard T2W MRI for accurate assessment of disease status (57,61).

According to Sun et al (6), who primarily looked at the change in ADC values to assess the tumour behaviour, significant increases in the tumour ADC occurred in the downstaged group. The increase in ADC was believed to be as a result of cellular insult resulting in cell death. This indirectly indicates the sensitivity of the tumour to chemo-radiation. They postulated that an early increase in ADC occurring by 1 week of CCRT could be a marker of tumour downstaging after chemo - radiotherapy. They concluded that early increase in ADC along with a low pre-treatment ADC value correlated with a good response to chemoradiation (14).

A similar observation was also made by Dzik-Juraz et al who noted that the pre-treatment ADC in the responder group was significantly lower than those that do not respond (55).

Some studies have however failed to demonstrate any benefit from ADC measurement pre and post CCRT (54,62).

Further on, a few studies have assessed diagnostic performance of conventional MR volumetry vs DWI in the prediction of complete response to CCRT (62). They performed volumetric signal intensity measurements. The results revealed that volume analysis on post-CRT DWI was more accurate than on T2W images for the prediction of complete response. The same conclusions were also drawn by few other studies (54,58).

Curvo-Semedo et al also noted that the volumetric measurements performed on post-CRT diffusion weighted images correlated well with the volume reduction measurements on T2W MR and DWI. They postulated that pre-treatment volume measurements may not be even necessary (57).

Overall, despite contradicting reports, DWI seems to be a promising tool for assessing response to treatment and deserves further study.

Technical considerations in performing DWI for rectal carcinoma (51,63)

For diffusion weighted imaging, the most widely employed technique is single shot (SS), spin echo (SE), echo-planar imaging (EPI) on 3T or 1.5T scanners with phased array coils. This has the advantage of high speed and increased signal-to-noise ratio.

A short TR (of around 1300msec) is used to decrease acquisition time. A TE of around 60-70msec is used. Three-four acquisitions are generally performed in a 128x192 matrix.

Some form of fat suppression is also required and STIR is most commonly used in body imaging to obtain uniform fat suppression.

Parallel imaging (GRAPPA –generalised autocalibrating partially parallel acquisition or SENSE – sensitivity encoding) is utilised to decrease distortion and ghosting artifacts.

Breath hold vs Free breathing

Farhood et al performed three different imaging sequences to identify the best sequence for abdominal diffusion weighted imaging – breath hold with parallel imaging, breath hold without parallel imaging and free breathing techniques with b-values of 50 and 1000. The signal-to-noise ratio was significantly higher for breath-hold acquitions. Breath-hold with parallel imaging at 3T had a higher image quality and lower artifacts (64).

Optimal b-value

B-value indicates the degree of diffusion weighting. A higher b-value is desired to obtain greater contrast. However, a very high b-value necessitates longer TE and lower signal to noise ratio resulting in image distortion. A low b-value on the otherhand (<100 sec/mm2) results in contamination of the ADC map by perfusion effect. Hence an optimal b-value needs to be determined (51,65).

DW MR images and ADC maps are most commonly acquired using b-values of 0 and 1000 sec/mm2 applied in x,y and z directions for pelvic applications(14).

While evaluating rectal lesions, to reduce errors in ADC calculation, some authors prefer multiple diffusion encoding with b values of 0, 100, 800 and 1000 sec/mm2 (13).

Different b values for use in gynaecological lesions has been studied. Visual scoring using b-values of 600,800 and 1000 were found to be successful for differentiating benign and malignant lesions. It was noted that the optimal b-values for evaluation of pelvic lesions are between 600 and 1000 sec/mm2 (66).

Accuracy of ADC value measurement – PACS vs dedicated workstation

A dedicated workstation is currently considered the reference standard to be used for calculating ADC values.

Traditionally, ADC values are calculated by exporting the diffusion images in a DICOM format to a separate offline MR workstation on which ADC maps were generated using three b values.

There are however many disadvantages in using a separate workstation, like increased time, disruption of normal work pattern resulting in underutilization of ADC measurements and reduced correlation with the rest of the imaging findings.

Studies have shown that there is no statistically significant difference in the ADC value measured from the PACS system and a specialised workstation (67).

The slight differences noted are presumed to be due to minor variations in the size and shape of the ROI placed.

MATERIALS AND METHODOLOGY

STUDY DESIGN: Study of diagnostic test accuracy

STUDY TYPE: Analytical

SETTING: Christian Medical College (CMC) Vellore is a tertiary care centre in northern Tamil Nadu. The institution was established in 1900 and is now a 2700 bedded hospital. The annual outpatient visits is around 1.9 million with inpatient admissions of ~ 120,000. The Department of Radiology in CMC, Vellore was established in 1936. Digitalization of the system and introduction of PACS (Picture Archival and Communication System) was done in the year 2000. The Department functions independently with around 80 radiologists. The radiological investigations routinely performed are radiographs, IVU, barium studies, ultrasonography and Doppler studies, mammograms, CT and MRI.

INCLUSION CRITERIA:

1) All the patients who presented to our Surgery department (Colorectal unit) with locally advanced rectal cancer (T3,T4) – ie clinical stage T3/T4 and any N or M stage
2) Those of the above who underwent chemo-radiation followed by surgery in our institution.
3) Those of the above who had an pre and post CRT MRI done in our institution prior to surgical resection

EXCLUSION CRITERIA

1) Previous CRT for rectal cancer or any other tumour of pelvis

2) Contraindication to MR imaging

3) Premature discontinuation of CRT

4) Delayed (more than 8 months after CRT) or cancelled surgery due disease progression or inoperable malignancy

5) Discontinued MR imaging examinations during therapy

METHODOLOGY

SAMPLING AND CONSENT:

The prospective study patients were referred to us from the surgical OPD or ward. All patients who fulfilled the inclusion criteria were included in the study. No specific sampling strategy was employed to enrol patients. The selection of the study population was independent of the results of the reference standard (histopathology). Baseline data of the patients was entered into a numbered proforma (Appendix 1). Informed written consent was obtained from the patient / patient's relative prior to the re-staging MRI. The consent form along with the Patient Information sheet is attached in Appendix 2.

TIMING:

The time period between the initial MRI and surgery would range between 6-8 weeks. The tumour in question is likely to significantly change in this period due to the effects of the chemo-radiation. The tumour may regress, remain same or progress. The degree of change in tumour characteristics in terms of signal intensity in usual MRI sequence and DWI will be assessed to predict TRG.

MAGNETIC RESONANCE IMAGING (MRI) EXAMINATION

a) MRI scanner

Pre and post operative MRI was performed at our institution in a 3T scanner (PHILIPS Achieva). MRI of the entire abdomen was performed at presentation for the initial staging. For re-staging following neoadjuvant chemoradiation, an MRI pelvis alone was performed in most of the cases. While doing so, an additional T2 SPAIR sequence of the entire abdomen was also done.

b) MRI coils

3T – SENSE-XL-Torso MRI coils were used

c) MRI protocol – Sequences and Technique

The MRI ABDOMEN and MRI PELVIS protocols included the following sequences – T2 coronal and axial; T2 SPAIR axial; T1 axial; T2 HR images – axial, coronal and sagittal; DWI with b values 0, 400, 800; ADC map.

(A) Localizer scan/Survey (sagittal, coronal and transverse planes)

(B) T2W coronal (Repetition time TR – 988ms; Echo time TE – 80ms; Flip angle – 90^0; slice thickness 6mm with slice gap 0.6mm; FOV 375mm; matrix 268x220; one acquisition scan time ~ 1.30minutes)

(C) T2W axial (TR – 941ms; TE – 80ms; Flip angle – 90^0; slice thickness 6mm with slice gap 0.6mm; FOV – 375mm; matrix 288x189; one acquisition scan time ~2 minutes)

(D) T2W SPAIR axial (TR – 782ms; TE – 70ms; Flip angle – 90^0; TI – 220ms; slice thickness 6mm with slice gap 0.6mm; FOV – 375mm; matrix 268x163; one acquisition scan time ~2 minutes)

(E) T1W axial (TR – 12ms; TE – 2.3ms; Flip angle – 15^0; slice thickness 6mm with slice gap 0.6mm; FOV – 380mm; matrix 256x153; one acquisition scan time ~1.37 minutes)

(F) T2W HR coronal (TR – 3546ms; TE – 80ms; Flip angle – 90^0; slice thickness 3mm with slice gap 0.3mm; FOV – 230mm; matrix 384x377; one acquisition scan time ~2.43minutes)

(G) T2W HR sagittal (TR – 3500ms; TE – 90ms; Flip angle – 90^0; slice thickness 3mm with slice gap 0.3mm; FOV – 220mm; matrix 352x273; one acquisition scan time ~2.23 minutes)

(H) T2W HR axial(TR – 3500ms; TE – 90ms; Flip angle – 90^0; slice thickness 3mm with slice gap 0.3mm; FOV – 230cm; matrix 368x291; one acquisition scan time ~3.19 minutes)

(I) Single shot EPI diffusion weighted transverse (Diffusion mode – 3 scan trace; Diffusion weightings – 3; b value 1 = 0; b value 2 = 400; b value 3 = 800; Trace weighted images; Average ADC maps; EPI factor – 77; TR – 3750ms; TE – 75ms; slice thickness 4mm

with slice gap 0.4mm; FOV – 380mm; matrix 128x116; one acquisition scan time ~3.15 minutes)

d) Image Interpretation

The imaging results was viewed and interpreted by the principal investigator with the help of two co-investigators with experience in pelvic MR imaging. The observers were blinded to patient's clinical data and pathology reports. The data was recorded on the proforma (Appendix 1)

The index test which is diffusion weighted imaging (DWI) was installed into the protocol for pelvic imaging.

1) For volumetric evaluation, the tumour outline was manually traced on each section. The tumour volume was calculated by summing all of the cross sectional volumes of the entire lesion. (Fig.3)
   For those tumours which were circumferential, the lumen of the rectum was included in the calculated volume to maintain uniformity among the observers. (Fig.4)
   On volumetry based on T2w scans, the hypointense areas after neoadjuvant therapy were also included in the measured tumour volume. This was due to the initial hypothesis stating difficulty in differentiating tumour tissue from fibrosis and the possibility of presence of viable tumour cells in regions of fibrosis.

2) The analysis of ADC is an automated process which is displayed as a parametric map. ADC measurements of a given region were recorded by drawing regions of interest (ROI) on the ADC map (Fig.2). The ADC values were initially measuring on the MRI workstation kept at the console and also at the PACS workstation. Paired sample T-test showed that:

- There is strong agreement between pre treatment ADC values measured in the MRI workstation and PACS workstation (r=0.959, p<0.0001). The values measured in PACS is 0.03+/-0.09 x 10^{-3} less than that measured on MRI WS and the difference is statistically significant (t=3.094, df=68, p=0.003). Though there is statistically significant difference between the two values the difference is too small to be clinically significant.
- There is strong agreement between post treatment ADC values measured in the MRI workstation and PACS workstation (r=0.91, p<0.0001). The difference between the mean ADC value measured in the MRI workstation and PACS workstation is not significant (t=1.043, df=19, p=0.310).

Hence, the subsequent ADC values were measured in the PACS workstation only.

The DWI Volumetry and ADC values were performed at a different time from the volumetry based on T2W MRI to eliminate bias. The results of the reference standard were not available at the time of interpretation of the index test.

In case of studies which did not show any areas of restricted diffusion after neoadjuvant therapy (ie complete response), the ROI's were placed in regions that showed residual tumour on T2w images.

3) The tumour regression grades (TRG) on T2w high resolution scans was assigned using standard criteria.

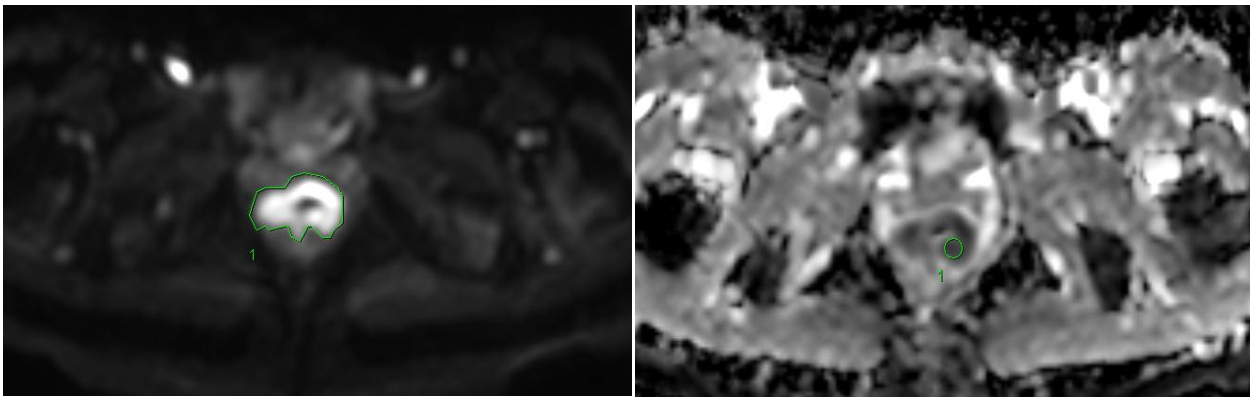


Fig.2a: DWI showing restricted diffusion within the lesion.	Fig.2b: Corresponding ADC map with the ROI placed within the tumour.

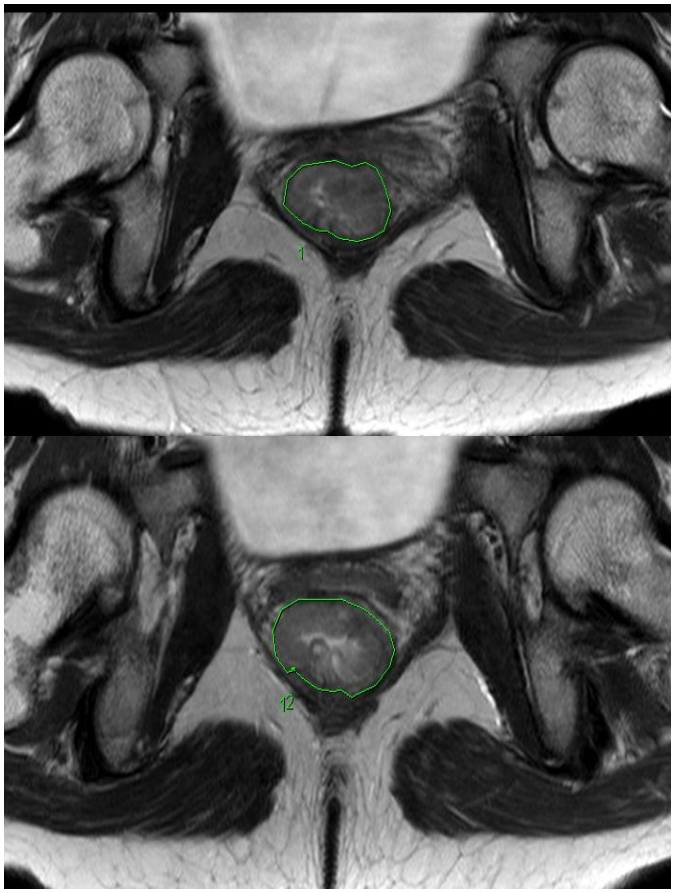


Fig.3a: Tumour volumetry as performed on T2-weighted HR axial scans

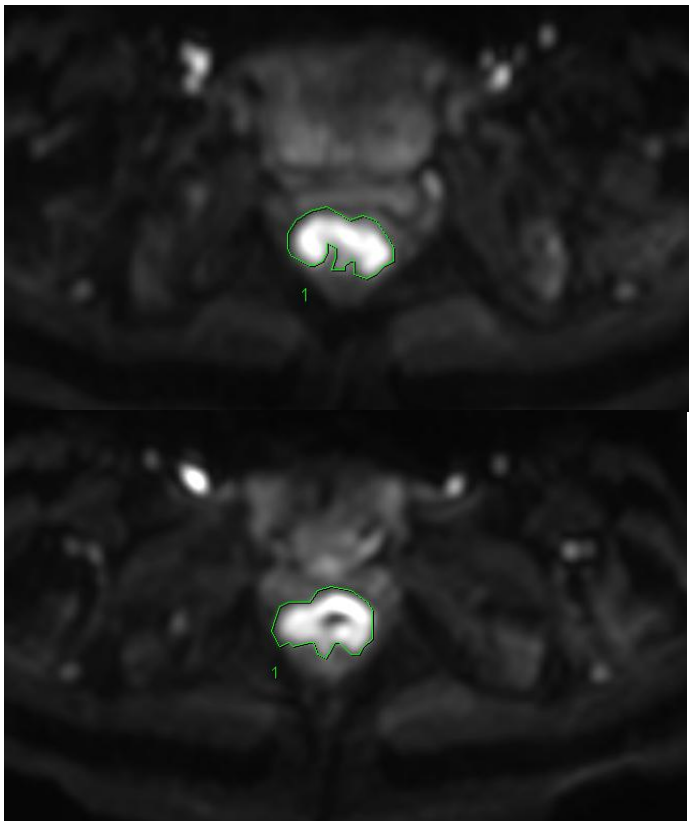


Fig.3b: Tumour volumetry as performed on DWI (b = 800)

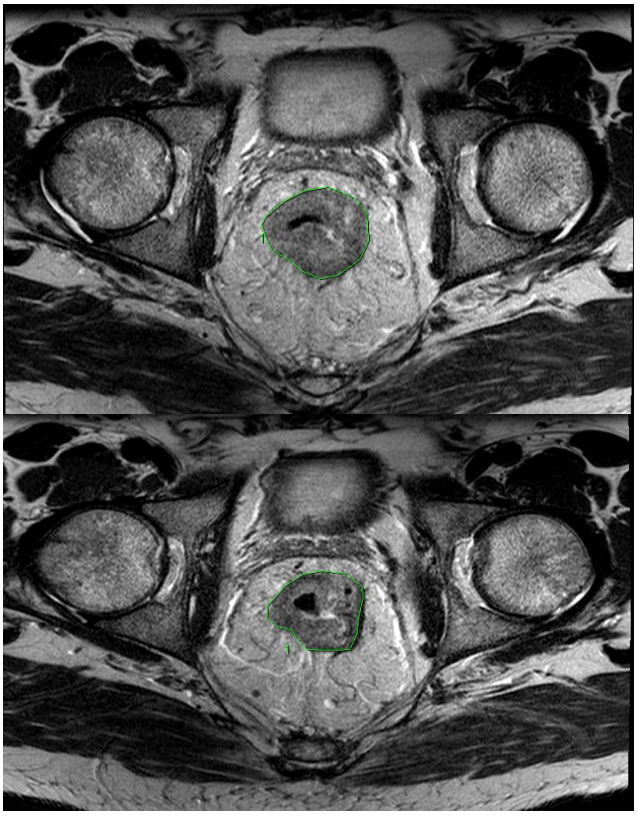


Fig.4: Tumour volumetry showing inclusion of the lumen in circumferential tumours

4) The tumour regression grades (TRG) on DWI were also assigned using the following criteria, adapted from RSNA based guidelines on appearances of various tissues on DWI (68).

TUMOUR REGRESSION GRADE	CRITERION
1	No residual diffusion restricted areas
2	A few scattered lakes of diffusion restricted areas
3	Predominant fibrosis (75%) with substantial diffusion restricted areas
4	Predominant restricted diffusion with minimal fibrosis
5	Tumour unchanged from baseline

Table.7: Tumour regression grading system based on DWI

e) Histopathological Examination:

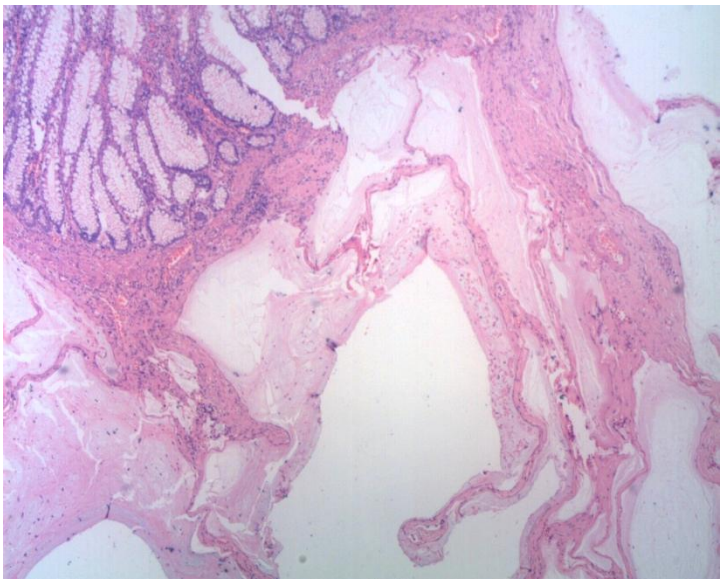
Histopathology was the standard of reference (gold standard). The slides were reviewed by two experienced pathologists with special interest in gastrointestinal pathology. Sections were checked for the presence of normal tissue, viable tumour, fibrosis, edema and any other relevant findings.

The tumour regression grade (TRG) was evaluated according to the method of Mandard et al. (38)

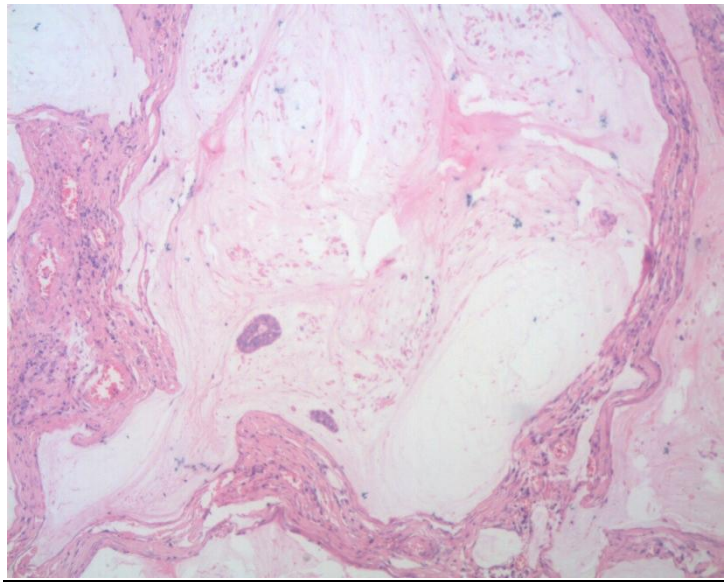
In addition, the following information was also provided

- the type of tumour
- circumferential resection margin
- vascular and perineural invasion
- involvement of resected lymph nodes
- pathological TNM stage (ypTNM)
- Description of the gross appearance of the main specimen included measurement and documentation of the following: Dimensions of the entire specimen, Location, dimensions and gross appearance of the tumour and distance of the tumour from the various resection margins

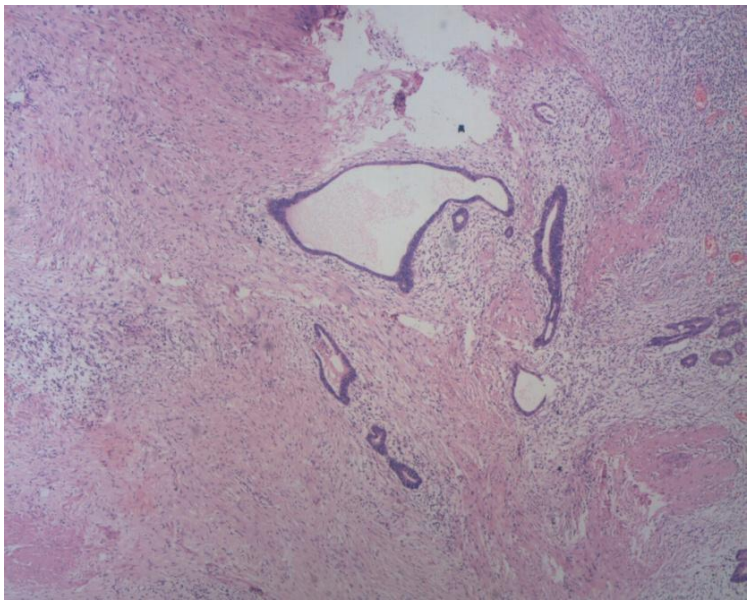
DEPICTION OF THE MANDARD'S TUMOUR REGRESSION GRADES



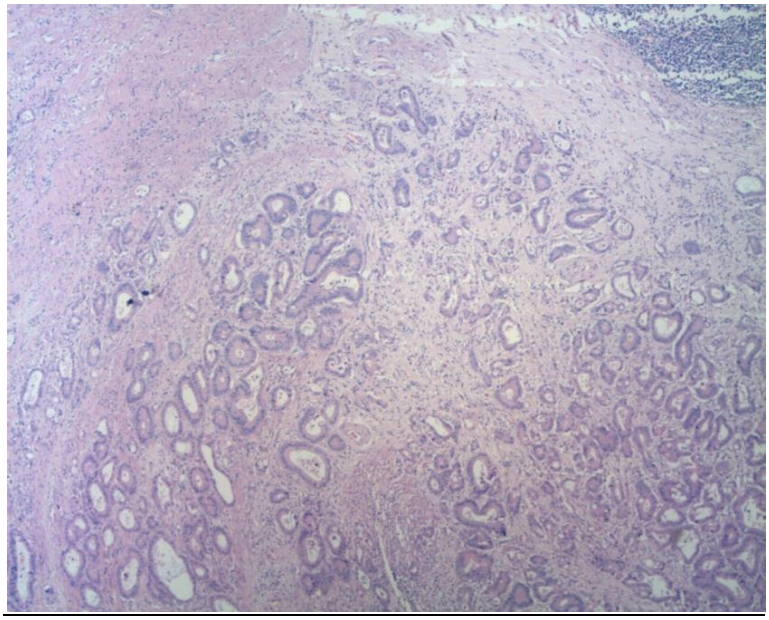
TRG 1: Absence of residual cancer and fibrosis extending through the wall (Complete regression)



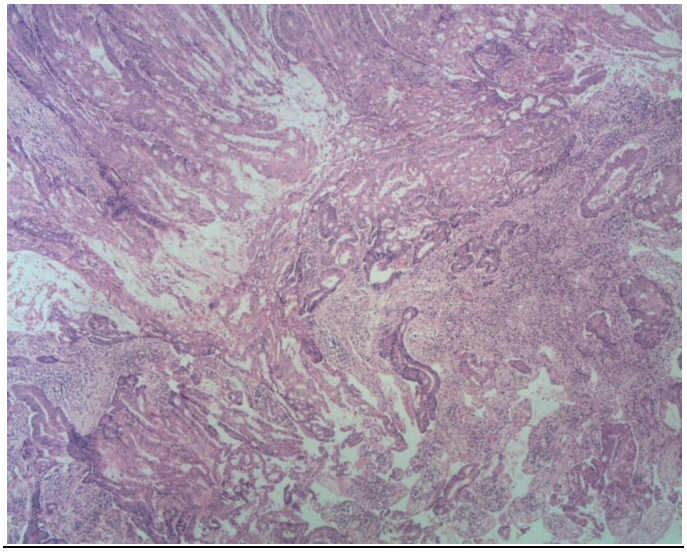
TRG 2: Rare residual tumour cells scattered throughout the fibrosis



TRG 3: Predominant fibrosis but increase in the number of cancer cells



TRG 4: Residual cancer cells outgrowing the fibrosis



TRG 5: Absence of regressive changes

INSTITUTIONAL REVIEW BOARD APPROVAL AND FUNDING :

Institutional review board (IRB) approval was obtained prior to the commencement of the study (IRB minutes number.7657 dated 18.11.2011) (Appendix 3).

STATISTICAL ANALYSIS:

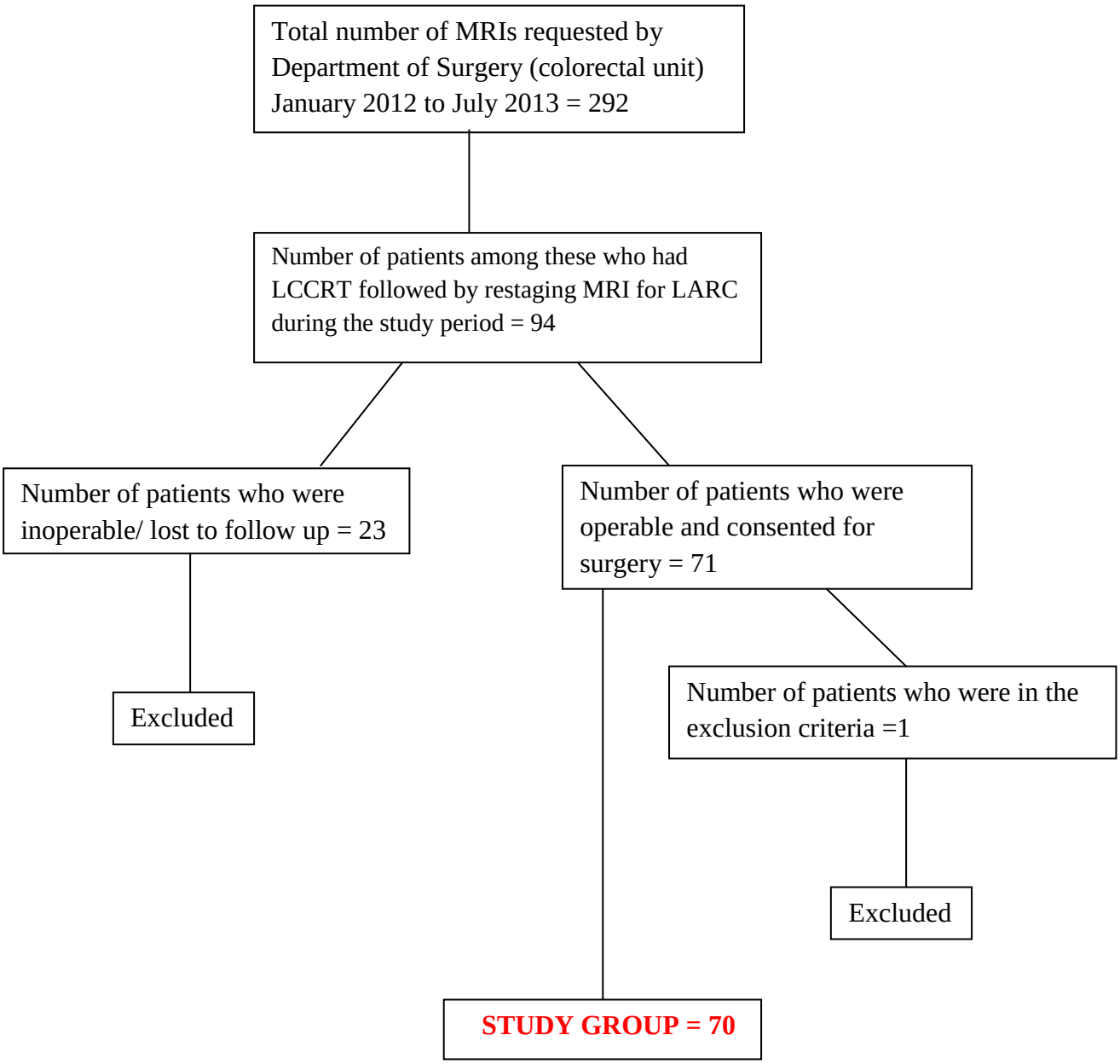
Statistical analyses were performed using SPSS software version 16. The changes in tumour ADC and volumes of the responder and nonresponder groups were analyzed using Wilcoxon ranksum/ Mann Whitney test.

Receiver operating characteristic (ROC) curves were employed to compare the diagnostic performance of tumour volume reduction rate and change in the ADC value for the prediction of complete response.

$P < 0.05$ was considered statistically significant.

ANALYSIS AND RESULTS

Flow chart of the progress through phases of study



(A) STUDY DESIGN

Duration of study

The study cases were prospectively recruited over a period of 20 months, from December 2011 to July 2013.

Sample size

A total of 292 patients with a clinical diagnosis of rectal cancer were referred from the Surgical department (Colorectal Unit) for MRI. Among these patients 93 came for restaging MRI of the pelvis following long course chemo-radiotherapy. Of these patients, 71 were operated. There others were either inoperable and were referred for palliative treatment or refused surgery or were lost to follow up.

1 out of the 71 patients was excluded because, the patient had MRI after excision of the malignant polyp and there was no significant abnormality in the initial MRI itself.

Hence, the total sample size was 70.

(B) PATIENT DEMOGRAPHICS

(i) Age Distribution

The mean age of the patient population was 49.24 years (range 23-74 years)

(ii) Sex Distribution

Of the 70 patients, 52 were male (74.3%) and 18 were female (25.7%).

(C) TUMOUR CHARACTERISTICS

(i) Tumour location

The majority of tumours were low rectal growths, comprising 64.3 % (45 in number).

27.1% were mid rectal tumours and 8.6% were upper rectal tumours (Fig.5).

(ii) Type of tumour

The most common tumour type was moderately differentiated adenocarcinoma comprising 72.9% (51 in number).

The other histological types were

- 12.9% mucinous and signet ring cell type

- 7.1% poorly differentiated adenocarcinoma

- 2.9% well differentiated adenocarcinoma

- Others : Squamous cell carcinoma, neuroendocrine tumour and high grade dysplasia. (1.4% in each type)

CLASSIFICATION OF TUMOURS BASED ON LOCATION

Fig.5a

Fig.5b

Fig. 5c

Classification of rectal tumours based on their location. Fig.5a depicts a low rectal growth

Fig.5b depicts an upper rectal tumour and Fig. 5c depicts a mid rectal tumour

(iii) Signal intensity of tumour

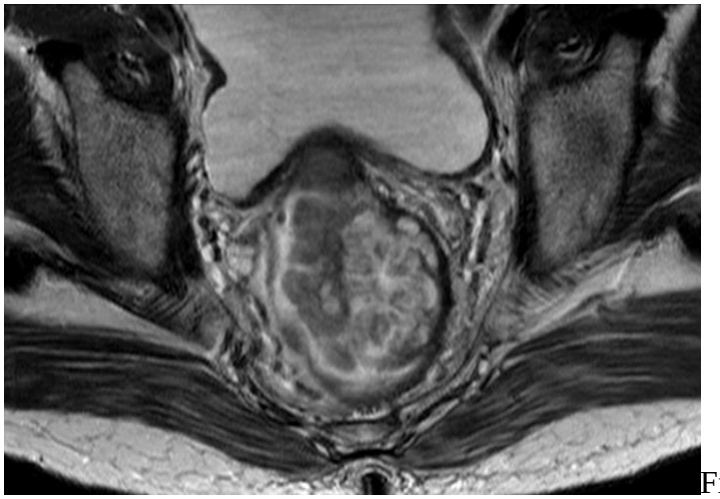
Most of the tumours had intermediate signal intensity on T2W images, accounting for 67.1% of the cases (47 in number). (Fig.6)

A significant number of lesions (15.7%) were hyperintense, suggestive of mucinous tumours. The remaining 17% had a mixed signal intensity containing both intermediate and hyperintense signal areas.

CLASSIFICATION OF TUMOURS BASED ON SIGNAL INTENSITY ON T2W IMAGES


Fig. 6a


Fig. 6b

 Fig. 6c

Classification of rectal tumours based on their signal intensity. Fig.6a depicts an intermediate signal intensity rectal tumour. Fig.6b depicts a hyperintense rectal tumour and Fig. 6c depicts a mixed signal intensity rectal tumour

D. <u>TREATMENT ADMINISTERED</u>

(i) Neoadjuvant therapy

All patients underwent neoadjuvant chemoradiotherapy (CRT)

Among these, a large subset of 66 patients (94.3%) was administered long course chemoradiation (LCCRT).

Three patients (4.3%) were given short course CRT due to associated co-morbidities. One patient (1.4%) received radical chemoradiation.

The LCCRT regime was given using a four field box with cobalt 60 gamma rays. ~5040cGy was administered in 28 fractions along with concurrent chemotherapy with Tab Capecitabine (at a dose of 825 mg/sq.m twice a day)

(ii) Surgery

Nearly equal number of adbomino-perineal excisions (APE) and low anterior resections (LAR) were performed, in 47.1% and 52.9% of the study population respectively.

(iii) Adjuvant therapy

91.4% of the patients were given adjuvant chemoradiotherapy.

The adjuvant treatment comprised various combinations of the following chemotherapeutic agents – 5-Fluorouracil, leukovorin, Oxaliplatin, Carboplatin, Etoposide, Capecitabine, FOLFOX regime and CAPOX regime.

The six patients who did not have adjuvant treatment were either lost on follow up or succumbed to the illness.

E. HISTOPATHOLOGICAL EVALUATION

(i) Distribution of pathologic regression after CRT

There were 13 patients (18.6%) who showed complete response to neoadjuvant treatment.

When the five categories are re-grouped into responders (TRG1 and 2) and non-responders (TRG 3-5), the percent in each group are 40% (n=28) and 60% (n=42) respectively.

The tumours were classified based on Mandard's tumour regression grading system

TUMOUR REGRESSION GRADE	FREQUENCY	PERCENT
1	13	18.6
2	15	21.4
3	21	30.0
4	18	25.7
5	3	4.3

Table.8: Frequency distribution of the study group based on the Mandard's tumour regression grading system into 5 categories

(ii) Circumferential resection margin (CRM)

The surgical specimen showed involvement of the CRM in 27.1%, while 72.9% had a negative CRM after surgery – defined as tumour to resection margin distance of >1mm.

F. MRI EVALUATION

The mean interval between MRI and Surgery was 11.8 days (SD 19.6)

(i) Distribution of pre – CRT stage on MRI (based on TNM classification)

Most of the patients had stage IIIb disease during initial presentation, comprising 74.3% of the study population. The TNM categories included in this stage are :

STAGE IIIb	T3-T4a	N1	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0

The other disease stages included Stage IIIc (11.4%), Stage IVa (7.1%), Stage IVb (4.3%) and Stage IIa (2.9%)

(ii) Distribution of post – CRT stage on MRI

Most patients continued to remain stage IIIb after neoadjuvant therapy; however the percentage had reduced considerably to 42.9%.

The tumour had responded variably and the stages fell into a wide category – Stage IIa (24.3%), Stage IIIa (12.9%), Stage IVb (5.7%), Stages I, IIIC and IVa (4.3% each), Stage IIc (1.4%).

(iii) Distribution of pre – CRT Circumferential resection margin on MRI

77.1 % (54 patients) had a positive CRM during the initial staging MRI. In the remaining 22.9%, the CRM was not involved.

(iv) Distribution of post – CRT Circumferential resection margin on MRI

In the post neoadjuvant therapy re-staging MRI, the number of patients with an involved CRM had reduced to 61.4 % (43 patients).

In 38.6% of cases, the CRM was not involved.

(v) Comparison between CRM determined on MRI and histopathology

There was good correlation between MRI and histopathology in determining involvement of CRM with a sensitivity of 89.4% (Pearson Chi - square value 8.657, df =1 and p value = 0.003).

However, when the CRM was negative, the performance of MRI was equivocal

There was fair correlation between the absolute measured value of CRM on T2W MRI and histopathology (R value 0.463, t = -4.5 and df =52)

G. TUMOUR VOLUME ANALYSIS

The median tumour volumes and their range in each pathological category of tumour regression grade is summarised in Table.9 and depicted in Fig.7

VOLUME mm3	TRG 1	TRG 2	TRG 3	TRG 4	TRG 5
Pre CRT –T2W	24 (7.7-61)	26 (8-97)	35 (9-122)	50 (6-134)	39 (25.9-49)
Post CRT – T2W	4.5 (2.8-8)	7.3 (1-93)	8.7 (1-85)	19 (10-55)*	18 (5-26)
TVRR T2W	81% (2-84)	57% (4-95)	71% (31-88)*	49% (9-59)*	54% (46-81)
Pre CRT –DWI	21.5 (5.5-54)	21 (6-98)	21 (9-62)	28 (6-102)	39 (30.7-56)
Post CRT – DWI	0 (0-3)	2 (0-90)	5 (1-33)	8 (1.5-88)	6 (5.5-31)
TVRR DWI	100 % (76-100)	75.7 % (±32)	80 (45-97)	56% (21-77)*	82% (45-84)

Table.9 * Interquartile range

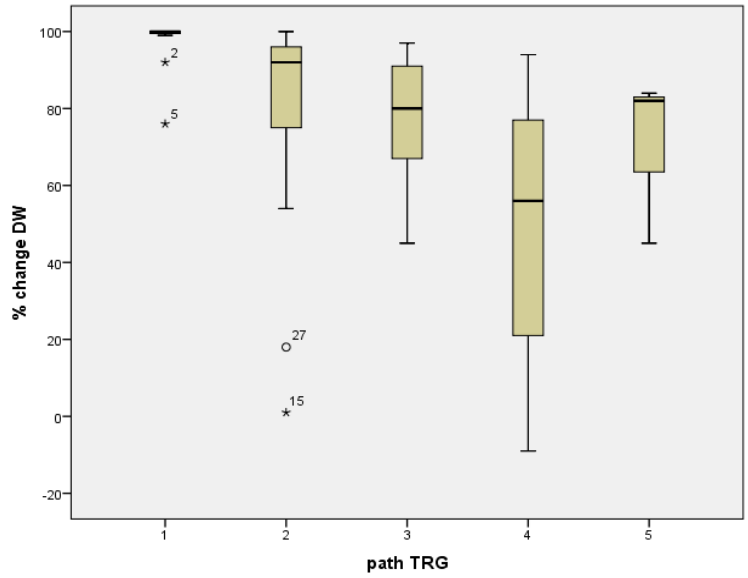


Fig.7a: Box and whisker plot of DW MR tumour volume change rate (TVRR) between the different TRG categories.

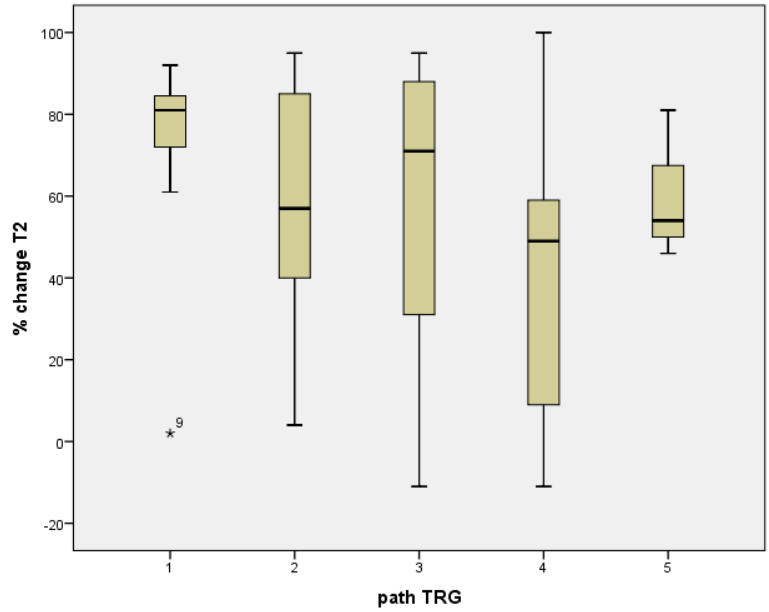


Fig.7b: Box and whisker plot of T2W MR tumour volume change rate (TVRR) between the different TRG categories.

For further analysis the patients were stratified into two groups based on the pathological TRG – the **complete response group (CR) and non-complete response groups (non-CR)**.

The initial tumour volume measured on T2-weighted MR images was not significantly different between the CR and non CR group, measuring 24 mm^3 (range 7.7-61) and 37 (6-134) mm^3 respectively (p=0.06).

After CRT, the tumour volume had reduced to 4.5mm^3(range 2.8-8) and 10 mm^3 (0-99) in the two groups (p = 0.002).

On DWI based MR Volumetry, the initial median tumour volume was not significantly different between the CR and non-CR groups, measuring 21.5 mm^3 (5.5-54) and 28.8 mm^3 (6-102) respectively (p=0.19).

On restaging after CRT, the median tumour volume had reduced to 0mm^3 (0-3) and 5mm^3(2-9.9)* in the CR and non-CR groups, respectively (p<0.001).

The post-CRT tumour volumes revealed a significant difference between the CR and non-CR in both T2-weighted and DW MR images (P<0.01).

The median reduction rate of tumour volume (TVRR) on DWI was 100% in the CR group and 77 % in the non-CR group (P < 0.001).

The median reduction rate of tumour volume (TVRR) on T2W MR images was 81% in the CR group and 58% in the non-CR group (P= 0.02)

Depiction of the range of values of the TVRR on T2 and DWI is as shown in Fig.8

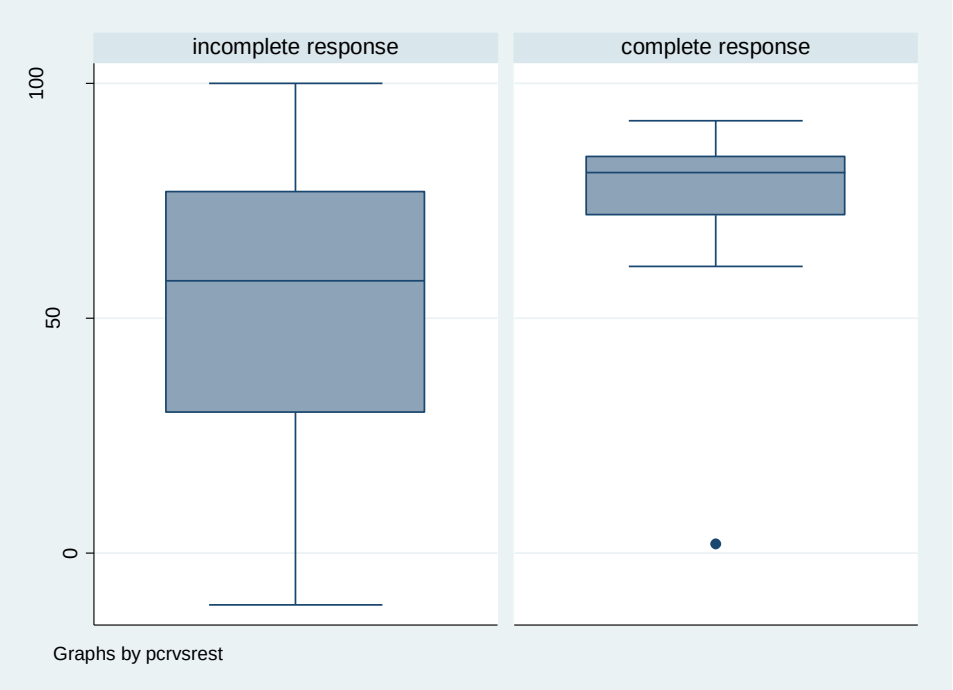


Fig 8a: Box and whisker plot of T2-weighted MR tumour volume change rate (TVRR) between the CR and non-CR groups (P = 0.02).
The box shows the range from the 25th percentile at the lower edge to the 75th percentile at the upper edge. The line across the box represents the median value. The whisker depicts the 10th and 90th percentile values.

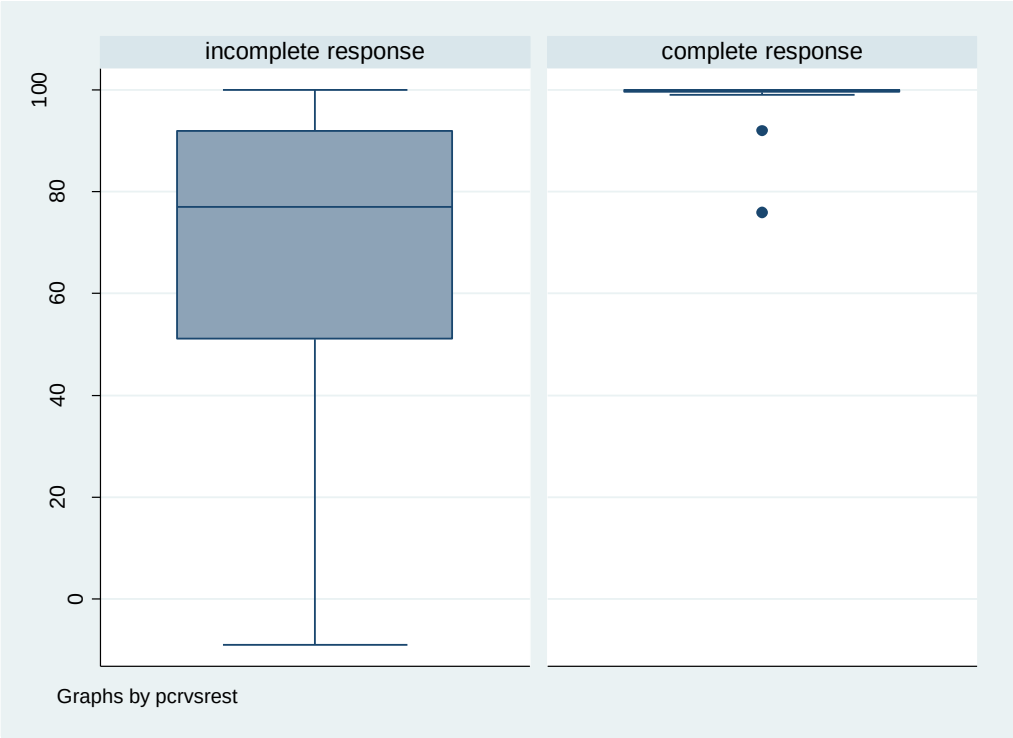


Fig.8b: Box and whisker plot of diffusion-weighted (DWI) MR tumour volume change rate (TVRR) between the CR and non-CR groups (P <0.001)

Further to increase the sensitivity, regrouping was done in a different manner – **responders (comprising TRG 1&2) and non-responders (TRG 3-5)**

In the subsequent analysis the parameters in tumour volumetry showing a significant difference between the responders and non responders was reduction rate of tumour volume (TVRR) on DWI. The median value was 96% in the responders and 73% in the non responders. ($p < 0.001$)

The post-CRT volumes on T2 and DWI also showed significant difference between the two groups ($p<0.01$).

H. ANALYSIS OF TUMOUR ADC

The mean ADC of the tumours in different TRG categories is as depicted in Table.10 and Fig.9

ADC ($\times 10^{-3}$ mm^2/s) (mean ± SD)	**TRG 1**	**TRG 2**	**TRG 3**	**TRG 4**	**TRG 5**
Pre CRT	0.936 (±0.24)	1.14 (±0.374)	0.854 (±0.118)	1.104(±0.429)	0.940 (±0.157)
Post CRT	1.49 (±0.2)	1.485(±309)	1.359 (±0.317)	1.378 (±0.387)	1.415 (±0.478)
TAIR	37% (±14)	23.25% (±18)	34.7% (±13.7)	21.24% (±9.8)	27% (±29)
Absolute increase in ADC	0.554 (±0.25)	0.344 (±0.28)	0.505 (±0.28)	0.272 (±0.12)	0.475 (±0.61)

Table.10: Mean ADC values - pre-CRT, post-CRT, Tumour ADC increase rate (TAIR) and absolute increase in ADC value (ΔADC) noted in the five TRG groups

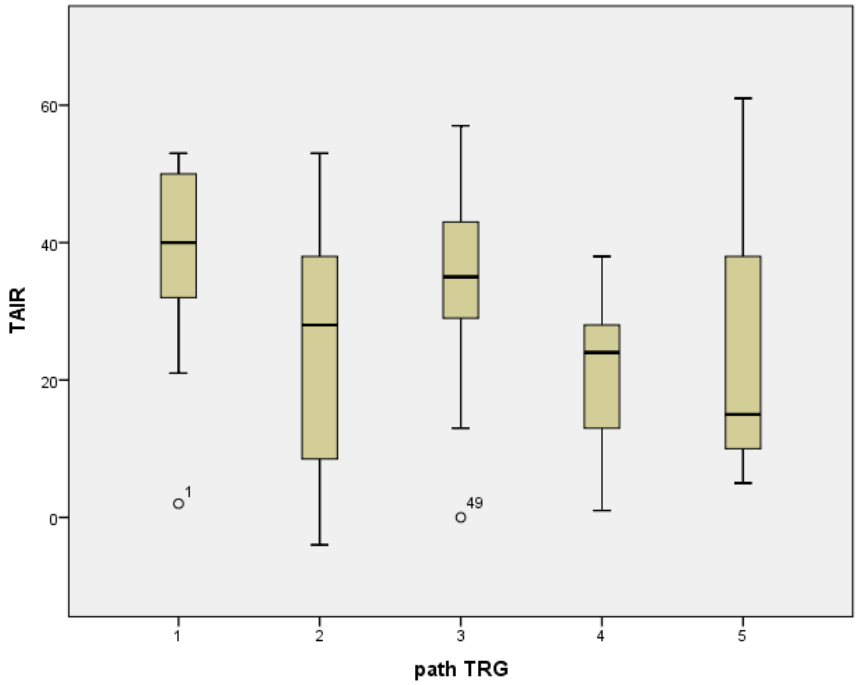


Fig.9: Box and whisker plot of Tumour ADC increase rate (TAIR) between the different TRG categories

For further analysis the patients were stratified into two groups based on the pathological TRG – the **complete response group (CR) and non-complete response groups (non-CR)**.

- The mean pre-CRT ADC for the CR group ($0.936\pm0.24\times 10^{-3}$ mm^2/s) versus the non-CR group($1.011\pm0.33 \times 10^{-3}$ mm^2/s) showed no statistically significant difference ($p = 0.49$).
- Similarly the mean post-CRT ADC for the CR group ($1.49\pm0.2\times 10^{-3}$ mm^2/s) versus the non-CR group($1.4\pm0.34\times 10^{-3}$ mm^2/s) also did not show statistically significant difference ($p = 0.114$)

However, the mean rate of ADC increase (TAIR-tumour ADC increase rate) between the CR group (37%) versus the non-CR groups (27.1%) showed a significant difference ($z= -2.149$, $p = 0.03$).

The absolute increase in ADC values were also different for the CR group (0.554±0.25× 10^{-3} mm^2/s) versus the non-CR group (0.39±0.28× 10^{-3} mm^2/s) (z= -2.286, p = 0.02).

Depiction of the range of change in TAIR (tumour ADC increase rate) and ADC values of the CR and non-CR groups are as shown in Fig.10

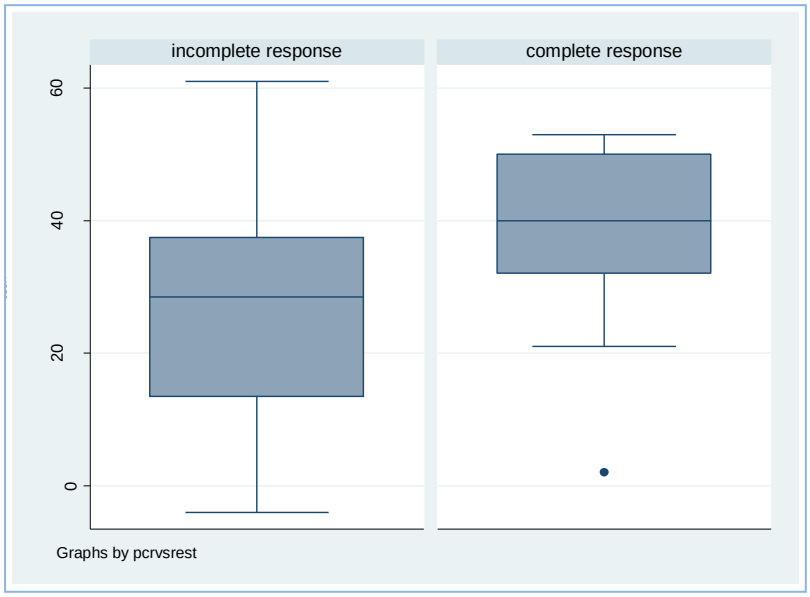


Fig.10a: Box and whisker plot of Tumour ADC increase rate (TAIR) between the CR and non-CR groups (P = 0.03).

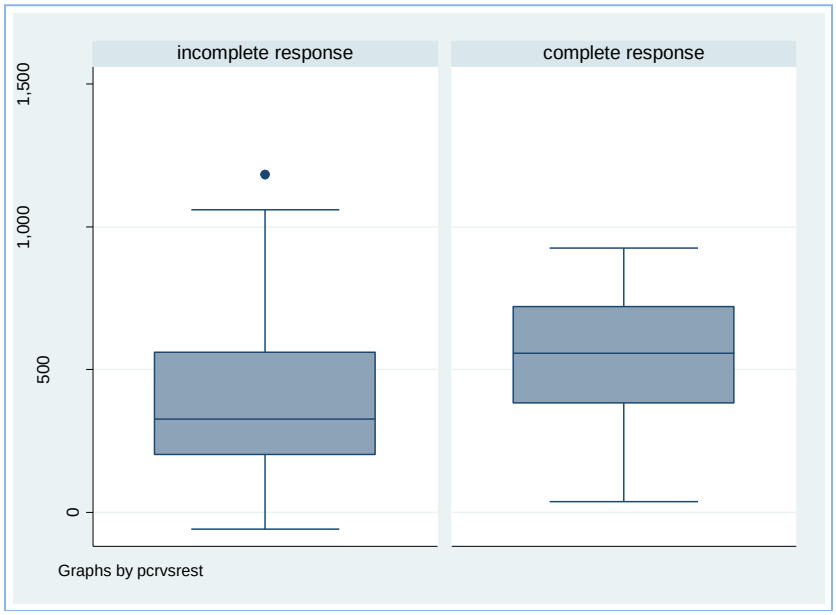


Fig.10b: Box and whisker plot of absolute increase in ADC value (difference) between the CR and non-CR groups (P =0.02)

I. COMPARISON OF THE DIAGNOSTIC ACCURACY OF DW MR VOLUMETRY, T2W MR VOLUMETRY AND ADC VALUES IN PREDICTING COMPLETE RESPONSE

ROC curves were used to compare the diagnostic performance of DW MR Volumetry, T2W volumetry and ADC values in predicting complete response.

The variables studied were the ones found to be of significance in the above described analysis – TVRR on DWI (ΔDWI), TVRR on T2W imaging (ΔT2W), TAIR and absolute difference in ADC (ΔADC).

The area under the curves (AUC) was measured to study the diagnostic accuracy of the tests. The corresponding data is shown in Table.11

The volumetry based on DWI (TVRR) had an AUC 0.921 and was superior to that based on T2W volumetry (AUC = 0.707). However, ROC curves showed that both the tests were good in assessing complete response Fig.11

For the post-CRT volumetric measurements, the AUC's were not significant and fell below the diagonal 0.5 line.

For the ADC measurements, The ROC curves of TAIR (tumour ADC increase rate) and absolute increase in ADC value (ΔADC) were obtained. The corresponding AUC were 0.692 and 0.704 (Fair), depicted in Fig.12

These values were better than that of the post-CRT ADC measurement alone (AUC 0.641)

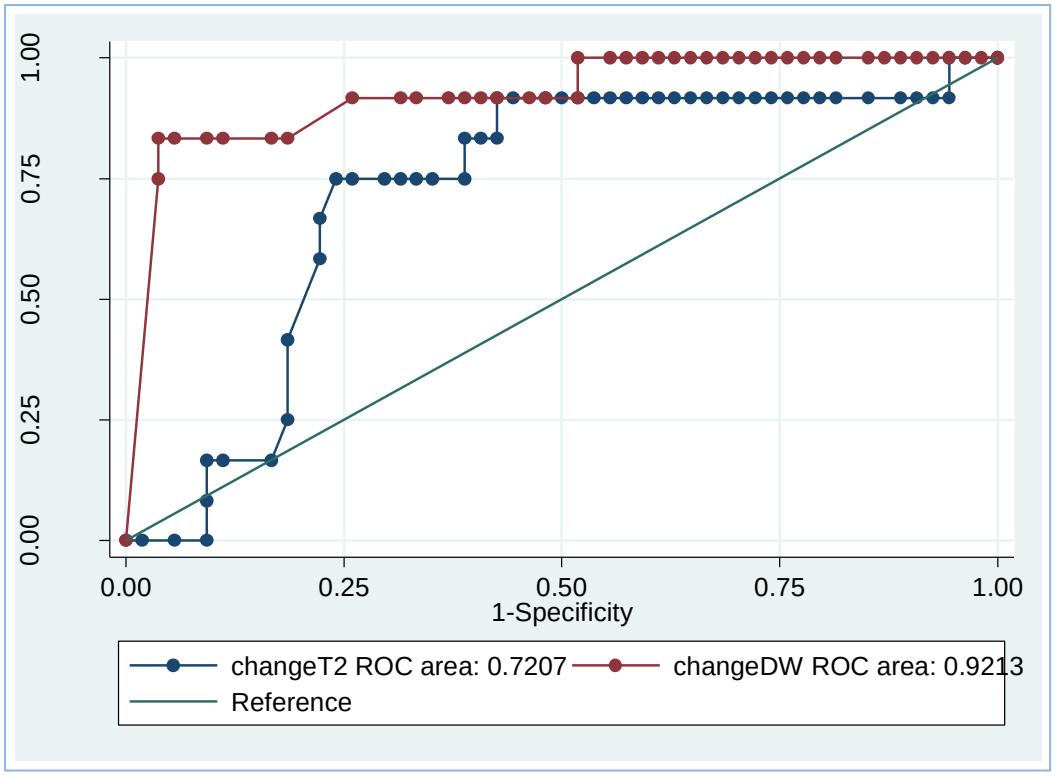


Fig.11: Comparison of ROC among DW MR volume reduction rate and T2-weighted MR volume reduction rate in predicting complete response

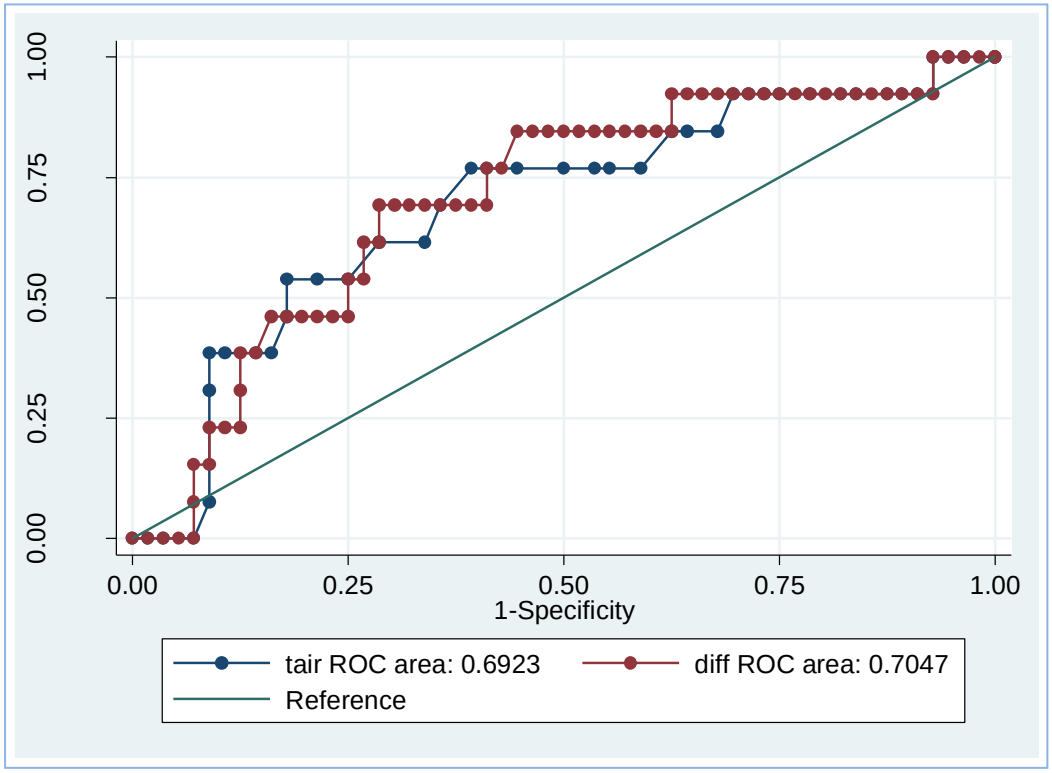


Fig.12: ROC curve depicting the diagnostic accuracy of TAIR and ΔADC in predicting complete response

Using optimal cut off values sensitivity and specificity of the different variables in predicting complete response was derived.

Tumour volume reduction rate on DWI with a cut off value of 94% had a sensitivity of 83.3% and specificity of 83.3%. The positive predictive value was 52.6% and negative predictive value was 95.7%.

	DWI MR volume reduction rate (%)	**T2W MR volume reduction rate (%)**	**TAIR**	**ΔADC**
AUC	0.921	0.72	0.692	0.704
Sensitivity %	83.3	75	53.8	69.2
Specificity %	83.3	74.5	82.1	71.4
PPV %	52.6	39.1	41.2	36
NPV %	95.7	93.2	88.5	90.9
Optimal cut off value	94%	77%	40%	$0.507x10^{-3}$ mm^2/s
P value	<0.001	0.017	0.032	0.022

Table.11: Comparison of the diagnostic accuracy of T2-weighted MR volume reduction rate, DW MR volume reduction rate, Tumour ADC increase rate and ΔADC in predicting complete response

J. COMPARISON OF TUMOUR REGRESSION GRADES ON MRI (MR-TRG) AND DWI (DW-TRG) WITH HISTOPATHOLOGICAL TRG (Based on Mandard's classification)

Agreement between the TRG as assessed using T2W MRI (MR TRG) and DWI (DW TRG) was determined by the kappa statistic (k < 0, poor agreement ,k 0-0.2, slight agreement; k 0.21to 0.40, fair agreement; k 0.41 to 0.60, moderate agreement; k 0.61 to 0.80,substantial agreement; and k 0.81 to 1.00, almost perfect agreement)

P less than .05 were considered significant.

(a) Agreement between MR TRG and histopathological TRG

Agreement	Expected Agreement	Kappa	Std. Err.	Z	Prob>Z
76.43%	68.55%	0.2505	0.0694	3.61	0.0002

(b) Agreement between DW TRG and histopathological TRG

Agreement	Expected Agreement	Kappa	Std. Err.	Z	Prob>Z
74.63%	66.31%	0.2469	0.0787	3.14	0.0009

There was fair agreement between the two classification systems based on MRI and Mandard's tumour regression grade. Also, both the classification systems performed almost equally in stratification into the tumour regression grades.

DISCUSSION

Locally advanced rectal cancer (LARC - T3, T4 lesions) is treated worldwide with primary staging using MRI followed by neoadjuvant chemoradiotherapy (CRT) and surgery. The prognostic factor assessing the response to CRT is given by the histopathological tumour regression grade (TRG), after surgery.

Restaging following CRT has hence become very important in planning and prognostication. The patients with a favourable response undergo definitive surgery followed by adjuvant treatment while those showing disease progression are either given further chemotherapy/palliative treatment. Studies have shown that in cases where there is complete regression of disease, a wait and see approach may also prove beneficial, thereby avoiding a major surgery and probable colostomy. This line of management has however not been adopted in our institution and all patients are advised definitive surgery.

Thus, the role of restaging has been emphasised upon.

In this study, we have looked at the role of diffusion weighted imaging (DWI) is assessing response to pre-operative chemoradiotherapy in patients with locally advanced rectal cancer.

RATIONALE BEHIND THE STUDY

Standard T2W high resolution MRI is a part of routine work-up to determine the extent of the tumour after CRT. However, there is difficulty in recognizing residual tumour in areas of radiation induced fibrosis. Also, following chemoradiotherapy, the tumour undergoes morphological changes like mucinous response, desmoplasia and fibrosis. It is difficult to visualize residual disease within these regions. Fig.13

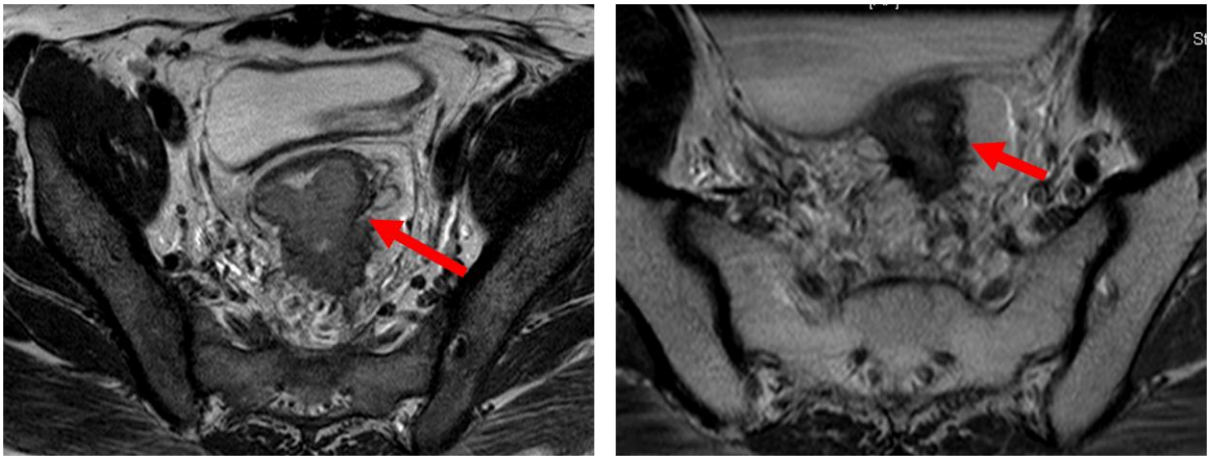


Fig.13a

TUMOUR FIBROSIS

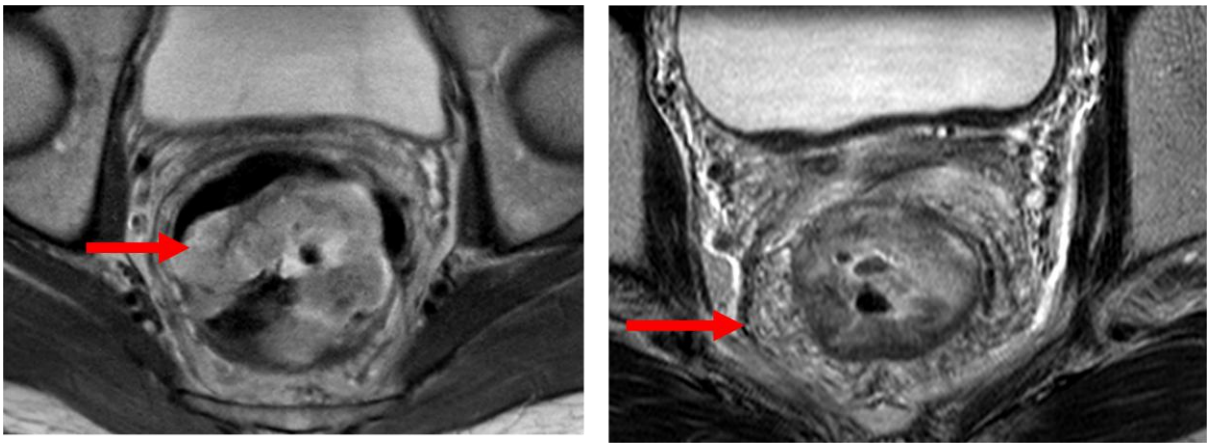


Fig.13b

TUMOUR DESMOPLASTIC CHANGE

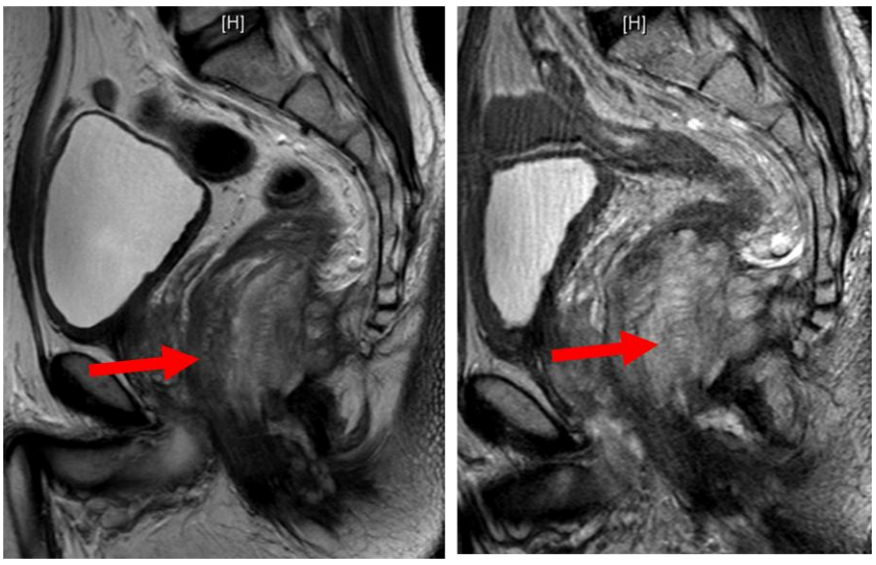


Fig.13c

TUMOUR MUCINOUS RESPONSE

Therefore, studies have looked at quantitative parameters like volumetry in assessing response.

Because of its promise in cancer imaging, we looked at the potential role of DWI in carcinoma rectum. Also, DWI is a noninvasive technique that does not require the use of ionizing radiation or contrast agents and can be easily added to any standard MRI protocol.

We have evaluated the diagnostic performance of DWI in predicting tumour response to chemotherapy and also compared it with standard T2W MRI. This was done by correlating with the pathological tumour regression grade - TRG (Mandard et al. tumour regression grades 1-5). For this, the diffusion weighted images obtained were evaluated in two aspects – (1) tumour volume using diffusion volumetry and (2) measurement of tumour ADC values.

As a secondary objective, we have also looked at MR tumour regression grade and its agreement with the histopathological tumour regression grade. We have also attempted to define a tumour regression grade based on DWI characteristics of various tissues (68).

A few studies done have shown DWI to have a higher sensitivity in detection of residual tumour, clearance of mesorectal fascia and also in identifying pathological complete responders. There has been no study till date which has looked at the role of DWI in predicting the tumour grade pre-operatively (TRG 1-5) in rectal cancers. Also there are few studies which have looked at quantitative assessment using DWI (ADC and volumetry), have shown promising results.

DISCUSSION OF RESULTS

DWI provides a good depiction of the primary tumour and residual disease/recurrence when used qualitatively in conjunction with T2W MRI. (Fig.14 and Fig.15)

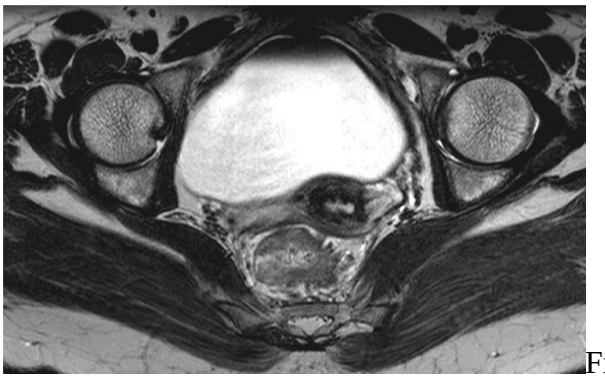


Fig.14a: T2W HR images showing a low rectal circumferential tumour.

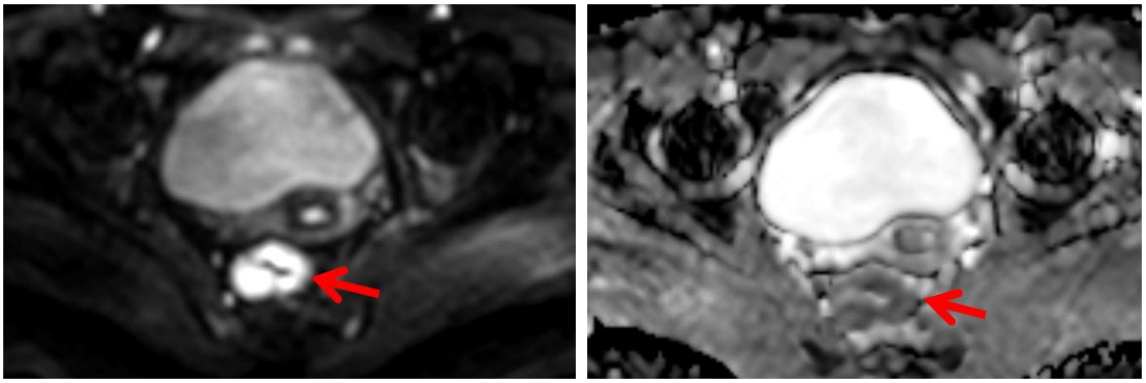


Fig.14 b,c: Corresponding DWI (b=800) and ADC map showing restricted diffusion within the lesion

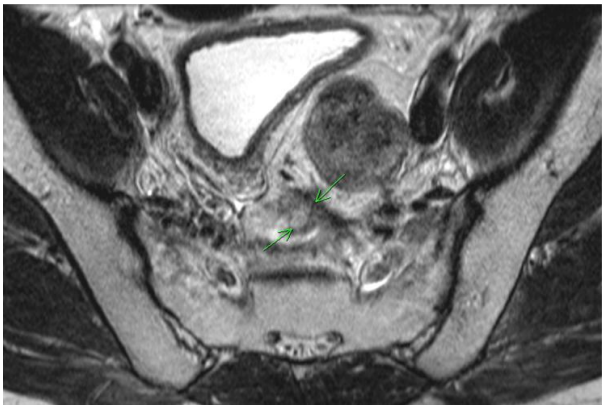


Fig.15a: T2W HR images showing tumour recurrence post operatively

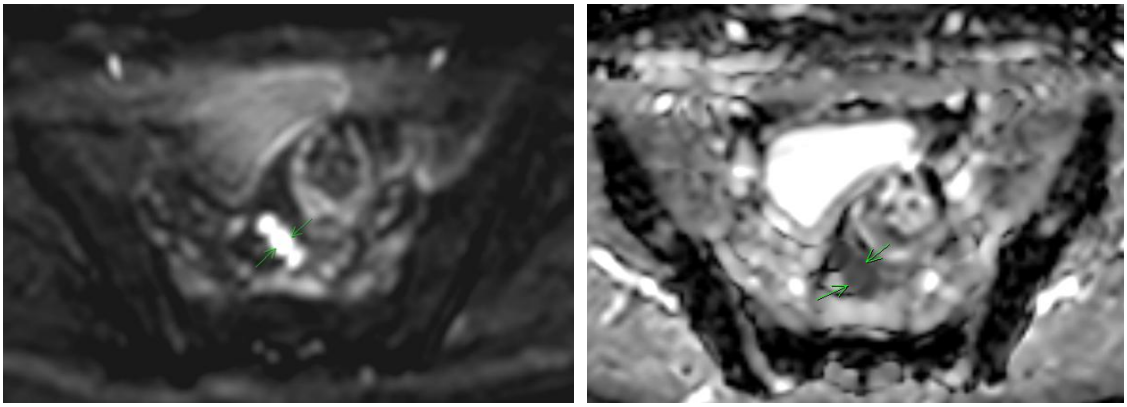


Fig.15 b,c: Corresponding DWI (b=800) and ADC map showing restricted diffusion within the recurrent lesion

(a) Volumetric analysis using DWI

The results of our study show that tumour volume reduction rate (TVRR) performed on DWI was the most consistently significant variable in determining response to CRT and fared better than TVRR based on T2w imaging.

We have depicted the range of values in each category of tumour regression grade as box plots (Fig.7). To compare the performance of DWI and T2w imaging, the TRG categories were subdivided into two groups – complete response (CR) group and non complete response (non-CR) group.

The volumetric variables found to be significantly different between the two groups were

- TVRR on DWI ($z = -4.551$, $p < 0.001$)
- TVRR on T2w ($z = -2.241$, $p = 0.025$)
- Post- CRT volume on DWI ($z = 4.731$, $p < 0.001$)
- Post- CRT volume on T2w ($z = 3.085$, $p = 0.002$)

Among these variables, the ROC curves indicated that TVRR based on DWI had a high diagnostic performance (AUC 0.92) for the assessment of complete response. The accuracy was more than that for TVRR based on T2W imaging (AUC 0.72).

For the post-CRT volumetric measurements on both DWI and T2W MRI, the AUC's were not significant.

The median volumes estimated on DWI were lower than those on T2W images in the post CRT images (5 vs 10 mm^3 in the non CR group and 0 vs 4.5 in the CR group) while the tumour volume reduction rates were higher (77 vs 58% in the non CR group and 100 vs 81 % in the CR group).

The probable reason for this could be our assumption that T2W imaging often overestimates residual disease by including areas of fibrosis as part of the tumour. Post RT related edema also creates a confusing picture in some cases. (Fig.16)

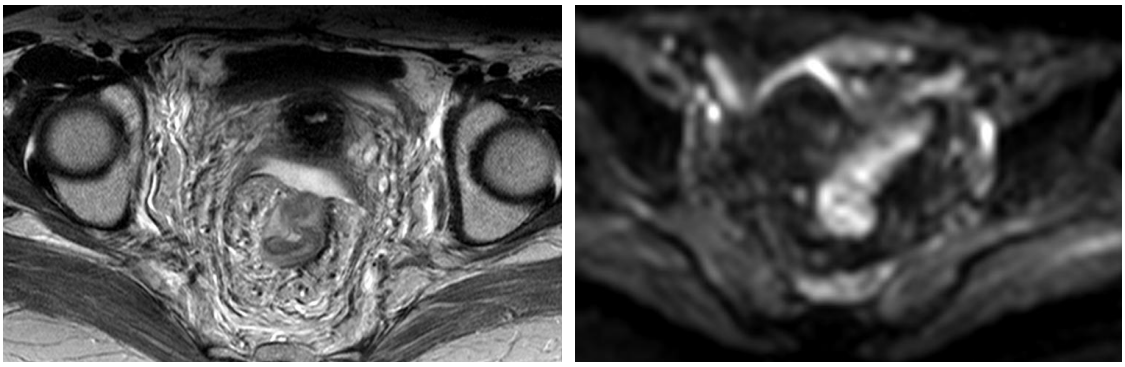


Fig.16a: T2w MRI showing post RT related edema which can mimic disease in certain cases. b: Corresponding DWI image

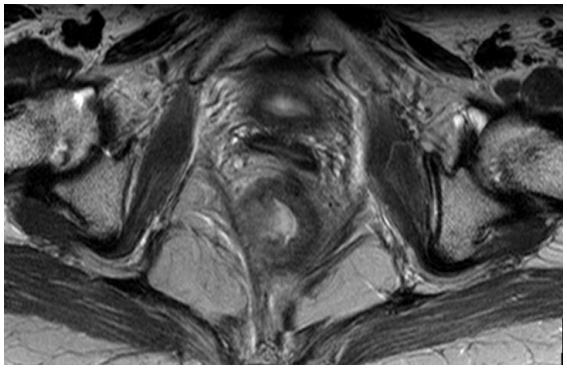


Fig.16c: T2W images of the same patient at the site of tumour shows lesion in the right lateral wall

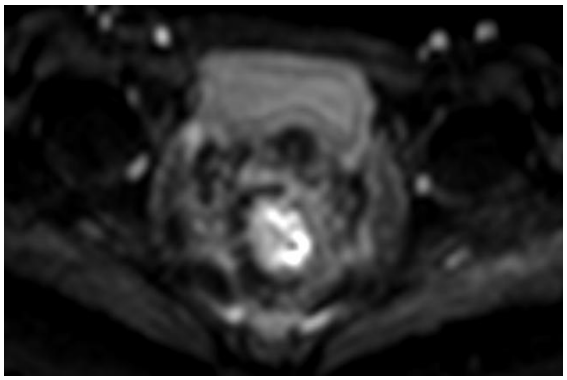


Fig.16d: Corresponding DWI images at the site of tumour

Our study showed that when 94% was used as a cut-off for TVRR based on DWI, the sensitivity and specificity for detecting a complete response were 83.3%. This also showed a high negative predictive value of 95.7%. Similarly when, 77% was used as a cut-off for TVRR based on T2W imaging, the sensitivity and specificity for detecting a complete response were 75% and 74.5% with a NPV of 93.2%. The results indicate that both DWI and T2w imaging can be used for ruling out a complete response, i.e. the presence of residual disease is well depicted on both, with DWI being more accurate.

With the high diagnostic performance of DW MR Volumetry, it can be hypothesized that a visual evaluation of whether or not a high signal intensity suggestive of residual tumour is remaining will be practical and less time consuming in day to day practice. Fig.17

Depiction of complete response

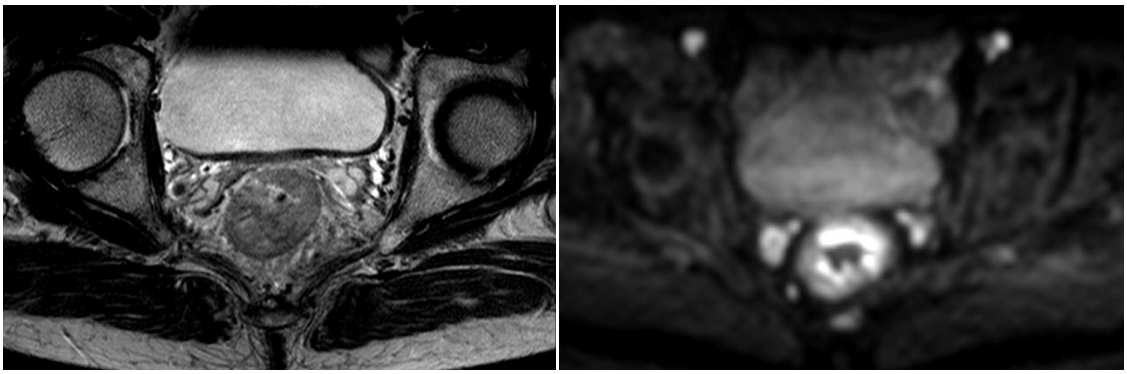


Fig.17 a and b: Rectal tumour prior to CRT on T2x and DWI

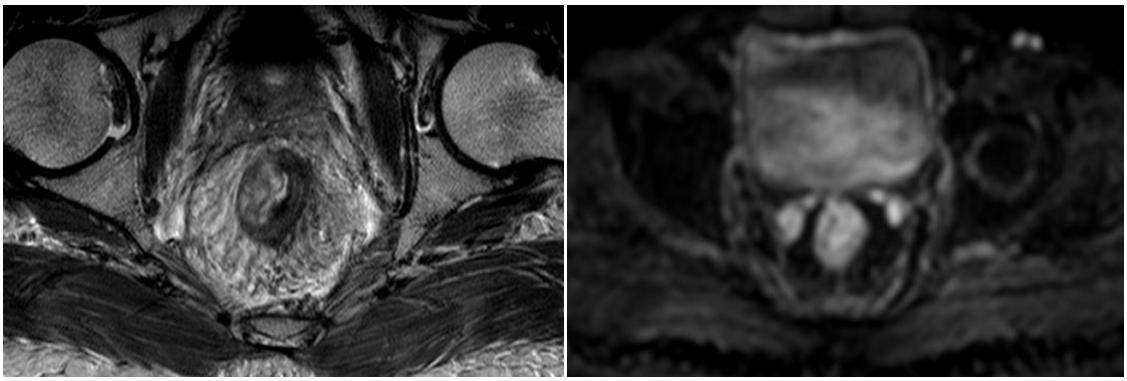


Fig.17 c and d: Post CRT images showing complete response, seen as fibrosis on T2w imaging and absence or restricted diffusion on DWI

Our results are in concordance with most studies that have shown benefit in performing TVRR for assessing disease response(46,49). Further, our study has also shown superiority of TVRR based on DWI when compared to T2w imaging (58,59).

However, we did not find benefit in assessing pre-CRT volumes and post-CRT volumes alone in depicting response to treatment.

(b) Quantitative assessment using ADC values

This parameter was studied under the assumption that post CRT, the tumour shows decrease in cellularity and would show an increase in the ADC.

The pre and post CRT ADC values as well as change in ADC values (absolute increase and percentage increase in value) were assessed in the different TRG categories.

Similar to the volumetric analysis, the categories were subdivided into CR and non-CR groups.

The variables found to be significantly different between the two groups were

- Tumour ADC increase rate (TAIR) ; ($z = -2.149$, $p = 0.03$)
- Absolute increase in ADC value (ΔADC); ($z = -2.286$, $p = 0.022$)

There was no significant difference between the groups in the pre-CRT and post-CRT ADC values.

On ROC curve analysis of the TAIR and ΔADC, the area under the curves were 0.692 and 0.704 which implied fair accuracy in predicting complete response.

These values were better than that of the post-CRT ADC measurement alone (AUC 0.641)

Optimal cut off points for these variables were TAIR - 40% and $\Delta ADC - 0.507 \times 10^{-3}$.

However, the sensitivity (53.8% and 69.2%) was low and specificity (82% and 71.4%) was moderate.

Hence, our study has shown beneficial results for change in ADC values (TAIR and ΔADC); the accuracy however being inferior to volumetric assessment of high b value images.

We did not find pre and post CRT assessment of ADC values useful in predicting response to treatment. This observation was contradictory to few studies which have shown a high post

CRT ADC and low pre-CRT ADC value to be helpful in predicting complete response(14,69).

This discrepancy may be related to the fact that a significant component of our study population comprised of mucinous/signet ring cell type of adenocarcinoma (~13%). These tumours demonstrate T2 shine through effect on DWI and in view of this, the ADC values are high both pre and post CRT. These tumours are also known to be resilient to CRT and occur in a younger population. Fig.18

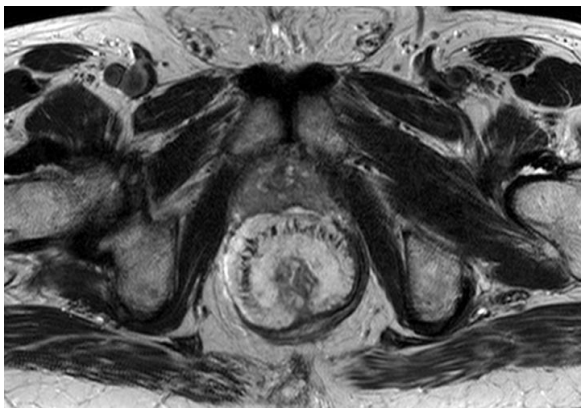


Fig.18a Mucinous adenocarcinoma appearing hyperintense on T2w axial image

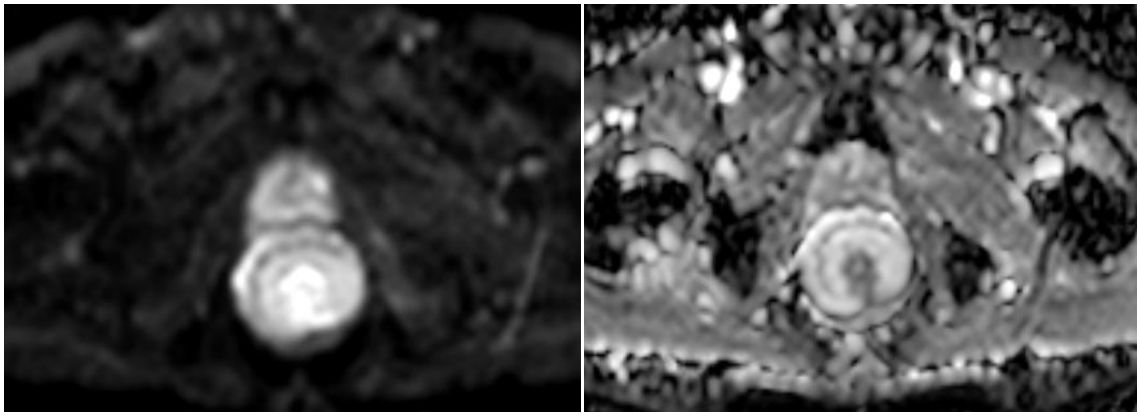
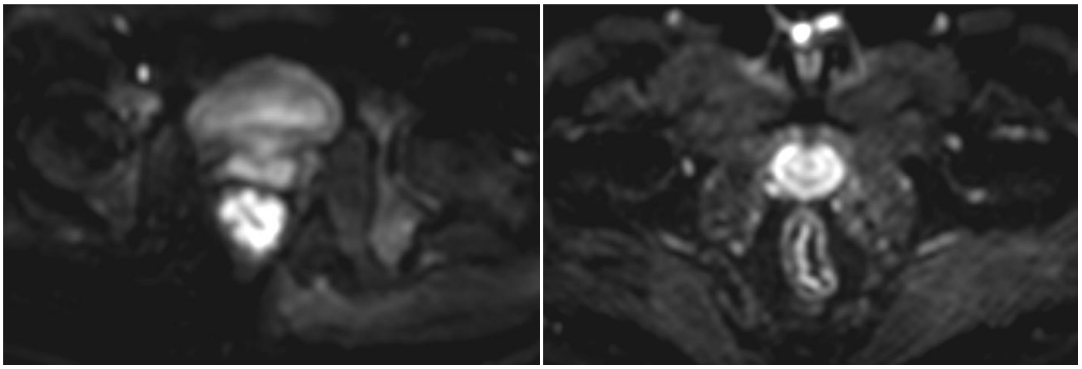


Fig.18b and c: DWI of the tumour demonstrating T2 shine through effect (facilitated diffusion

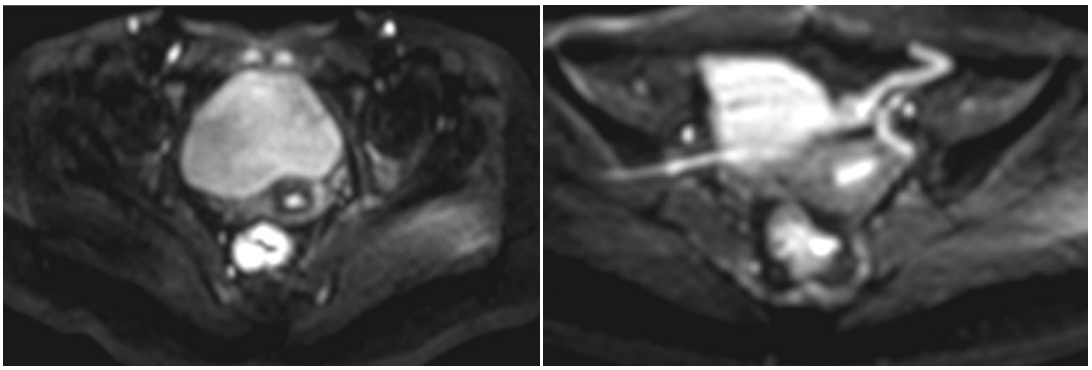
(c) Tumour regression grading on T2W MRI and DWI

The MRI tumour regression grade based on T2W imaging showed good agreement with the histopathological tumour regression grades. This was in concordance with the MERCURY trial(42). Hence TRG can be used as a prognostic indicator for disease recurrence and survival.

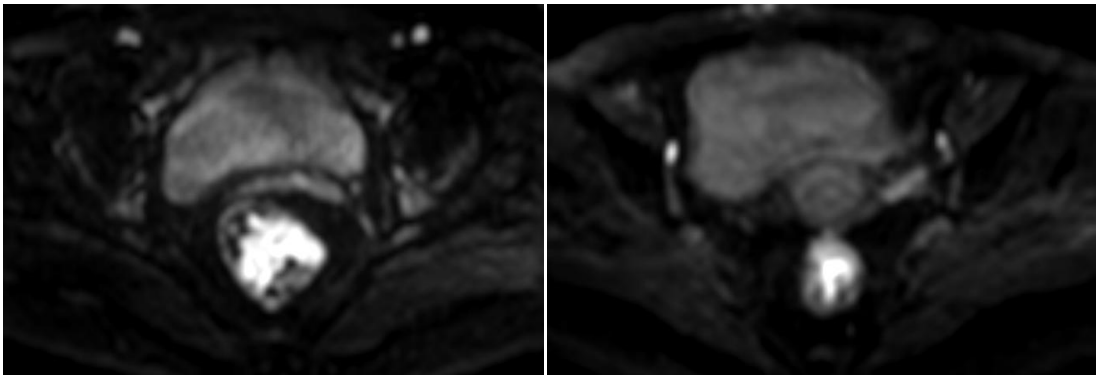
We had also graded tumour response using DWI using similar criteria based on the assumption that residual tumour would show restricted diffusion compared to fibrosis and hence the amount of tumour and fibrosis from the baseline scan can be compared (Fig.19). This again showed good agreement with histopathological tumour regression grades. Thus, the use of DWI in conjunction with T2W HR MRI would help in providing an accurate TRG.



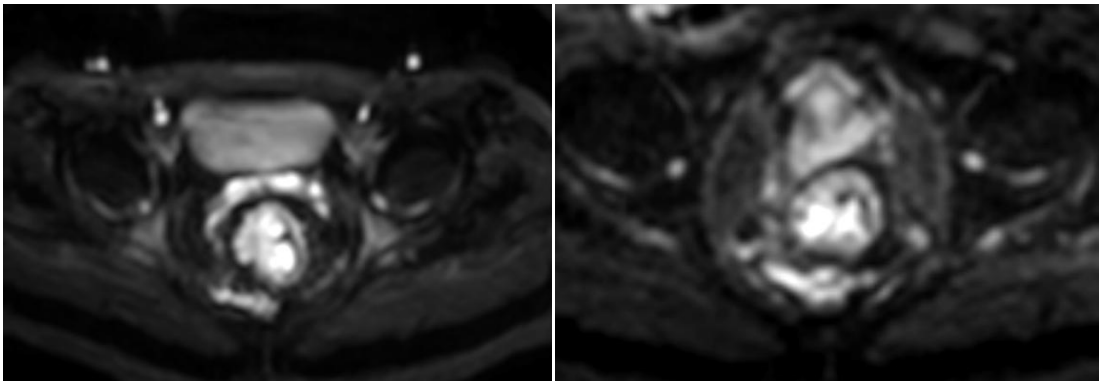
TRG 1 – No residual tumour



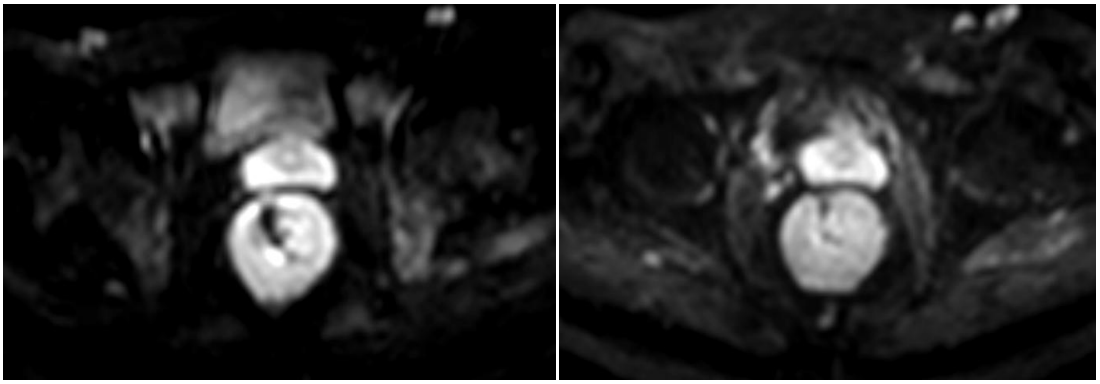
TRG 2 : Scanty lakes of restricted diffusion (viable tumour)



TRG 3: Predominant fibrosis with substantial diffusion restricted areas



TRG 4 - Predominant restricted diffusion with minimal fibrosis



TRG 5 – No change from baseline

Fig.19: Tumour regression grades based on diffusion characteristics of tissues.

The first image in each set shows the pre-CRT appearance and the accompanying image shows the post-CRT appearance.

LIMITATIONS

This study was subject to few limitations

1. Some of the studies had interpretation difficulties due to artifacts and the DWI protocol had to be gradually tailored to obtain optimum image clarity.

2. Since our study had a substantial number of mucinous tumours, the assessment of mean ADC may not be accurate. These tumours demonstrate T2 shine through effect rather than diffusion restriction.

3. Another reason for falsely assuming restricted diffusion is when the rectal lumen contains fluid, especially layered along the dependent wall. This was carefully interpreted by cross referring with the ADC map.

2. Some of the patients did not have MRI done according to protocol. Most of these cases were done either as an emergency or in the late hours.

3. The regimes used for CRT were not uniform among all patients. This is probably not important because we did not evaluate the efficacy of the treatment regimen but assessed the DWI tumour volumetry and ADC change as predictive factors of tumour regression.

4. A direct correlation between preoperative MR images and surgical specimen was not possible as the actual histopathologic tumour volume could not be obtained. This was not done due to specimen shrinkage and changes in appearance during transport and storage.

CONCLUSIONS

1. MRI due to its excellent soft tissue resolution and multiplanar imaging capability is an established modality to image rectal carcinoma. T2-weighted high resolution scan performed perpendicular to the axis of the tumour is the current investigation of choice in initial staging.
2. When it comes to restaging after neoadjuvant chemoradiotherapy, the accuracy of T2W imaging is lower due to the inability to confidently distinguish residual tumour from fibrosis, desmoplasia and identify viable tumour within mucinous components.
3. DWI is an emerging modality and is useful in re-staging rectal cancer after neoadjuvant chemoradiotherapy prior to surgery. Qualitative as well as quantitative analysis can be done. Quantitative parameters include volumetry and ADC values.
4. Tumour volume reduction rate (TVRR) performed on DWI as well as T2W imaging are both useful in assessing complete response. The accuracy of DWI volumetry (AUC 0.92) is more than that of T2W volumetry (AUC 0.72).
5. A cut-off value of 94% for the tumour volume reduction rate on DWI and 77% on T2W imaging predicts complete response with high accuracy (AUC 0.833 and 0.748 on DWI and T2W respectively).

   Both and these tests also have a high negative predictive value (95.7% and 93.2% on DWI and T2W respectively). This would indicate that both DWI and T2W imaging can be used for ruling out a complete response, i.e. the presence of residual disease is well depicted on both, with DWI being more accurate.
6. In view of the high diagnostic performance of DW MR Volumetry, it can be hypothesized that a visual evaluation of whether or not restricted diffusion suggestive of residual tumour is remaining will be practical and less time consuming in day to day practice.

7. On ADC analysis, the tumour ADC increase rate (TAIR) and absolute increase (ΔADC) among the CR and non-CR groups though statistically significant as a predictor of response was inferior to tumour volumetry on DWI (AUC 0.7 vs 0.92 for ADC and volumetry respectively).
8. Tumour volumes measured either on pre-CRT or post-CRT T2w and DW images were not beneficial when used alone for assessment of response.
9. Pre and post CRT assessment of ADC values were not accurate in predicting response to treatment. Unlike other studies, this finding could be due to the high incidence of mucinous tumours in our population which do not demonstrate restricted diffusion.
10. Tumour regression grade (TRG) assessed using T2w MRI as well as DWI are in good agreement with histopathological tumour regression grade.
11. In conclusion, considering the high diagnostic performance of TVRR based on DWI, the use of DWI in conjunction with T2W MRI will be useful in assessing response to treatment. Tumour regression grade assessed using T2W MRI and DWI can be used as a prognostic marker for disease recurrence and overall survival.

In daily practice, T2W high resolution scans could be used as a reference for tumour location. DWI in combination with T2W MRI could lead to more accurate detection of residual tumour, despite the relatively low spatial resolution and image quality of DWI alone.

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APPENDIX 1

Christian Medical College, Vellore
Department of Radiodiagnosis

A study on role of diffusion weighted MRI in assessing the response to chemo radiotherapy in patients with locally advanced rectal cancer

PROFORMA

Serial no:

1. Name: 2. Sex: 3. Age: 4. Hosp no:
5. Referring unit

Clinical information

1. Clinical history and findings:
    - Duration of symptoms:
    - Findings on examination:
    - Rectoscopy /Sigmoidoscopy findings:
    - Colonoscopy findings:

2 Pre-CRT stage on 1st MRI (T2W):

3 Biopsy report:

4 Type and duration of chemo-radiation:

5 Duration between CRT and surgery:

6 Duration between restaging MRI and surgery:

7 Type of surgery performed:

8 Has the patient discontinued CRT / not undergone surgery (cause):

3. Histopathology

1 Histopathologic diagnosis
   - Well differentiated adenocarcinoma-1/ moderately differentiated adenocarcinoma-2 / poorly differentiated adenocarcinoma -3 / mucinous adenocarcinoma -4 / signet ring cell carcinoma -5

2 Postoperative histopathologic stage:

3 Tumour size (gross specimen):

4 Tumour regression grade (1-5):

5 Pathological complete response(TRG 1) or incomplete response(TRG2-5) :

4. MRI

1. Pre chemoRT MRI:

Site: 1- low/ 2- mid/ 3- high rectum

	T2W	DWI
T Stage		
CRM		
N Stage		
M stage		
Volume of tumour		
ADC value: 1st ROI		
2nd ROI		

3rd ROI		
Mean		

2 . Post chemoRT MRI:

Site: 1- low/ 2- mid/ 3-high rectum

	T2W	DWI
T Stage		
CRM		
N Stage		
M Stage		
Volume of tumour		
ADC value – 1st ROI		
2nd ROI		
3rd ROI		
Mean		

Is the result unclear due no remaining high signal intensity tumour tissue :

% reduction in volume (T2W):

% reduction in volume (DWI):

Change in ADC:

APPENDIX 2

INFORMED CONSENT

Department of Radiodiagnosis, Christian Medical College, Vellore

A study on role of diffusion weighted MRI in assessing the response to chemo radiotherapy in patients with locally advanced rectal cancer

Information sheet

You are being requested to participate in a study to see if a new MRI technique called diffusion weighted imaging (DWI) can help in assessing the response to chemo-radiation before you undergo surgery. Presently the response can only be accurately assessed after the surgery by microscopic evaluation of the tumour tissue. By preoperative imaging using this special technique, we may be able to get an idea about the prognosis of this disease at an earlier stage.

How does DWI help in assessment after chemo-radiotherapy?

We have observed that there is difficulty in identifying tumor tissue amidst post radiation changes using routine MRI scan. However with the help of DWI, the tumour tissue can be identified as bright areas and easily differentiated from post radiation changes. However, we have only used this for a few people and we need to use it on more people to be sure that it really helps.

Does DWI have any side effects?

There are no known side-effects. This additional scan will take 2 minutes of the total scan time and will be a part of routine MRI.

If you take part what will you have to do?

If you agree to participate in this study, there will be no change in the other treatments and investigations that you will be having. You will be expected to come for the initial MRI and the repeat MRI after chemo radiotherapy as advised by your doctor. No additional blood tests will be done as a part of this study.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

What will happen if you develop any study related injury?

This scan does not involve injections or radiation and it is completely non invasive. So, we do expect any procedure related injury. However you can immediately report to us.

Will you have to pay for the DWI?

You will **not** be charged for this additional scan. All other investigations, as requested by your doctor will continue in the usual manner.

What happens after the study is over?

You may or may not benefit from this study. Once the study is over, if we come to a conclusion that the investigation is beneficial, we will be able to use this sequence in assessing and prognosticating patients in future. Your doctor may also use this on you again to detect recurrence if required.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission.

CONSENT TO TAKE PART IN THIS STUDY

Study Title: *A study on role of diffusion weighted MRI in assessing the response to chemo radiotherapy in patients with locally advanced rectal cancer*

Study Number:
Participant's name:
Date of Birth / Age (in years):

I_____,son/daughter of
_____
Declare that I have read/been read to the information sheet provided to me regarding this study and have clarified any doubts that I had. [ ]

(Please tick boxes)
I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access
[ ]

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:
Signature/thumb impression
Date:

Name of witness:
Relation to participant:
Date:

APPENDIX 3

ABSTRACT

Objective: To assess the role of DWI in predicting response to neoadjuvant chemoradiotherapy in patients with locally advanced carcinoma rectum (LARC) compared with T2W imaging. Secondarily, to evaluate the accuracy of tumour regression grade (TRG) assessed using MRI (T2W and DWI) in comparison with histopathological TRG.

Methods: A prospective analysis of 70 patients with LARC, who underwent neoadjuvant CRT and subsequent surgery was done. All patients underwent pre- and post-CRT T2W MR and DWI. The tumour volumes on T2W and DW images, difference in tumour volumes, pre and post-CRT ADC, difference in tumour ADC were measured. The TRG on T2W MRI and DWI were independently assessed. Histopathologic tumour regression grade was the standard of reference. The diagnostic accuracy of the tests in predicting complete response was compared using ROC analysis. The agreement between the MR tumour regression grades and histopathology was assessed using kappa statistic.

Results: The range of volumetric and ADC values in each TRG category were derived. The groups were subdivided into complete response (CR, n=13) and non-CR groups. Tumour volume reduction rate (TVRR) calculated on DWI and T2W MR were both useful in assessing complete response, with the accuracy of DWI being superior (AUC 0.92 for DWI vs 0.72 for T2W). The tumour ADC increase rate (TAIR) and absolute increase (ΔADC) though statistically significant as a predictor of response was inferior to tumour volumetry on DWI (AUC 0.7). Using a cut-off value for the tumour volume reduction rate of more than

94% on DWI, the sensitivity and specificity for predicting CR was 83.3% with NPV of 95.7%.

There was fair agreement between the TRG based on MRI (76.4%, kappa 0.25, $p < 0.01$) /DWI (74.6%, kappa 0.24, $p < 0.01$) and histopathological TRG

Pre- and post-CRT volumetry, ADC values when viewed independently were not reliable.

Conclusion: The parameters found to be of significance in assessing response to neoadjuvant CRT are tumour volume reduction rate - TVRR on DWI and T2W, tumour ADC increase rate – TAIR and ΔADC. Among these, volumetry based on DWI was superior with high diagnostic accuracy in predicting complete response. TVRR based on T2W and changes in ADC values had similar diagnostic accuracies.

Tumour regression grade assessed using T2W MRI and DWI are also useful as prognostic markers for disease recurrence and overall survival.

APPENDIX 4

DATA SHEET: PAGE 1

ID	sex	Age	NA Rx	Surgery	Interval	Adj	Site:	Signal	pre TNM	pre stage	pre CRM
099864F	M	33	1	1	6	1	1	1	T3N1M0	7	0
101843F	M	56	1	1	90	1	1	1	T3N2M0	7	1
092469F	M	64	1	1	34	1	1	3	T3N2aM0	7	1
108200F	M	29	1	2	2	1	3	1	T3N1M0	7	0
104455F	M	47	1	1	2	1	1	1	T3N1M0	7	1
112468F	F	30	1	2	16	1	2	2	T3N1M0	7	1
111464F	M	35	1	1	1	1	1	1	T3N1M0	7	0
121410F	M	52	2	1	33	1	1	1	T3N1M1	9	1
129140F	M	65	1	1	7	1	1	1	T3N2M0	7	1
125228F	M	44	1	1	3	1	1	1	T3N2M0	7	1
416436A	M	53	1	2	104	1	1	1	T3N2M0	7	0
142308F	F	25	1	2	7	1	2	1	T3N1M0	7	1
119193F	M	37	1	2	16	1	2	1	T3N2M0	7	1
775021B	M	71	1	2	4	1	2	1	T3N1M0	7	0
152437F	F	40	1	1	6	0	1	1	T3N2M0	7	1
428039	M	74	1	1	5	1	1	1	T3N1M0	7	0
175137F	M	69	1	1	2	1	1	3	T3N2M0	7	1
169046F	F	35	1	1	2	1	1	1	T4bN3M1a	9	1
173122F	M	35	1	1	22	1	1	1	T3N2M0	7	1
178661F	M	36	1	2	2	1	2	3	T3N1M0	7	1
185111F	F	51	1	2	4	1	1	1	T3N1M0	7	1
031803F	M	70	1	2	2	1	2	3	T3N2M0	7	1
192335F	F	73	2	1	37	0	1	1	T3N2bM0	8	1
197008F	F	36	1	2	7	1	1	3	T3N2bM0	8	1
208487F	F	54	1	1	6	1	1	2	T3N2aM0	7	1
123375F	F	48	1	2	2	0	2	1	T3N1M0	7	0
208919F	F	41	1	1	6	1	1	1	T3N1M0	7	1
225966F	M	45	1	2	6	1	2	3	T3N2M0	7	0
229471F	M	56	1	2	34	1	2	1	T3N1M0	7	1
223437F	M	54	1	1	1	1	1	1	T3N2aM0	7	1
264554F	M	33	1	2	6	1	1	2	T3N2M0	7	1
266897F	M	43	1	2	3	1	3	2	T3N1M0	7	0
285223F	M	37	1	1	2	1	1	2	T3N1M0	7	1
283177F	M	37	1	2	1	1	1	1	T3N2aM0	7	0
276207F	F	58	1	2	6	1	2	1	T3N2M0	7	0
268764F	M	30	1	1	6	1	1	3	T3N1M0	7	1
206757F	M	63	1	2	86	1	2	3	T3N1M1b	10	1
030220d	M	35	1	1	5	1	1	2	T3N2aM0	7	1
165994F	M	29	1	2	7	1	2	1	T3N2aM0	7	1
287766F	M	25	1	2	5	1	2	1	T3N1M0	7	1
303908F	M	63	1	2	2	1	2	1	T3N2M0	7	0
284895F	M	60	1	2	8	1	1	1	T3N1M1a	9	1
131845F	M	57	1	2		1	3	2	T3N1M0	7	1
286035F	M	51	1	2	6	1	1	1	T3N2M0	7	1

Data sheet: page 2

post TNM	post stage	post CRM	MR CRM	pre ADC	Post ADC	ΔADC	pre vol DW	post vol DW	TVRR DW
T2N0Mx	2	0	4	0.72	1.024	304	5.64	2.74	51.41844
T3N1M0	7	0	4	0.901	1.432	531	35.08	2.857	91.85576
T3N2Mx	7	1	0	1.316	1.906	590	98.1	25	74.5158
T3N0Mx	3	1	0	0.841	1.295	454	15.8	1.004	93.64557
T3N0M0	3	1	0	0.814	1.198	384	25	0	100
T3N1Mx	7	1	0	1.078	1.27	192	39.31	6.3	83.97354
T2N1Mx	6	0	4	0.845	1.566	721	32.45	0	100
T3N0M1	9	0	2	0.789	1.096	307	14.16	0.52	96.32768
T3N1M0	7	0	3	0.683	1.238	555	36.64	7.384	79.84716
T3N2Mx	7	1	0	0.952	1.462	510	33.67	1.15	96.5845
T3N1M1	9	0	3	0.769	1.95	1181	55.89	30.63	45.19592
T2N1Mx	6	1	0	1.0787	1.24	161.3	13.3	3.94	70.37594
T3N2Mx	7	1	0	0.643	1.508	865	52.386	8.932	82.94964
T3N1M0	7	0	4	1.14	1.731	591	5.517	1.34	75.71144
T3N2Mx	7	1	0	0.916	1.217	301	29.68	9.873	66.73518
T3N0M0	3	1	0	0.892	1.23	338	16.144	3.656	77.35382
T2N1Mx	7	1	0	0.96	1.528	568	42.34	3.024	92.85782
T4N3M1a	9	1	0	0.969	1.196	227			
T3N2Mx	7	1	0	1.14	1.275	135	28.19	22.37	20.64562
T3N1M0	7	1	0	1.23	1.416	186	58.67	11.42	80.5352
T2N0M0	2	0	2	0.923	1.848	925	8.66	0	100
T3N1M0	7	1	0	1.097	1.205	108	57.354	15.542	72.90163
T2n1M0	6	0	3	0.8	1.293	493	8.693	4.803	44.74865
T3N1M0	7	0	2.5	0.787	1.151	364			
T3N1M0	7	1	0	1.569	1.834	265	76.97	83.89	-8.990516
T2N1M0	6	0	13	0.906	1.222	316	13.23	5.107	61.39834
T3N0M0	3	1	0	0.59	0.892	302	15.98	7.97	50.12516
T3N1M0	7	0	7	0.971	1.693	722	61.816	33.44	45.90397
T3N0M0	3	1	0	0.774	1.281	507	17.685	0	100
T3N1M0	7	1	0	0.903	1.491	588	19.095	6.92	63.76015
T3N2M0	7	1	0	1.275	1.228	-47	91.426	90.369	1.156126
T3N1M0	7	0	7	1.579	1.616	37	17.645	0	100
T3N1aM0	7	1	0	1.523	1.465	-58	6.8	3.15	53.67647
T3N1Mx	7	0	2	0.898	1.253	355	16.098	8.4	47.8196
T3N1Mx	7	0	16.5	0.821	1.758	937	18.185	0	100
T3N0M0	3	1	0	1.306	1.71	404	7.967	2.44	69.37367
T3N1M1b	10	1	0	0.995	1.586	591	34.279	7.872	77.0355
T3N1Mx	7	1	0	2.114	2.376	262	65.94	63.63	3.503185
T3N0M0	3	1	0		1.384	1384	43.156	3.43	92.05209
T2N1M0	6	1	0	0.833	1.176	343	15.914	1.24	92.20812
T2N1Mx	6	0	10	0.861	1.262	401	35.509	3.2	90.9882
T2N1M0	6	0	3	0.927	2.11	1183	15.596	0.925	94.06899
T3N0M0	3	1	0	1.385	1.498	113			
T3N1M0	7	1	0	0.933	1.239	306	11.25	3.125	72.22222

Data sheet: page 3

pre vol T2	post vol T2	TVRR T2	MR TRG	DW TRG	path TRG	CR	Histo	Path CRM	CRM mm
5.613	5.213	7.12631	3	4	4	0	1	0	6
36.69	5.83	84.1101	1	2	1	1	2	0	3
85.73	78.55	8.37513	5	5	2	0	4	1	0
13	14.4	-10.7692	4	2	3	0	2	1	1
30.25	3.09	89.7851	2	1	1	1	2	0	
38.522	17.616	54.2703	4	3	5	0	2	0	7
26.02	3.79	85.4343	2	1	1	1	2	0	
20.04	1.448	92.7745	3	2	2	0	2	0	
44.5	11.88	73.3034	4	4	3	0	2	0	15
34.23	6.39	81.3322	4	2	3	0	2	0	3
49.28	26.382	46.4651	4	3	5	0	2	1	0
15.97	9.378	41.2774	3	2	3	0	2	0	3
67.346	5.004	92.5697	3	3	3	0	2	0	3
17.65	2.8	84.136	4	2	1	1	1	0	
34.06	8.728	74.3746	4	4	3	0	2	0	4
22.083	9.949	54.9472	4	2	4	0	2	1	1
40.042	5.9	85.2655	3	2	2	0	2	0	
21.16	1.008	95.2363	2		2	0	3	1	0
56.73	62.75	-10.6117	5	4	4	0	3	1	0
98.12	43.34	55.8296	4	3	4	0	2	0	8
19.359	7.643	60.5197	2	1	1	1	2	0	
69.938	40.85	41.5911	4	3	4	0	3	0	2
25.826	10.407	59.7034	4	3	3	0	2	0	3
			3	4	4	0	2	0	2
63.321	68.432	-8.07157	5	5	4	0	4	1	0
9.043	7.227	20.0818	3	3	3	0	2	0	10
31.511	29.083	7.70525	3	2	3	0	2	0	2
60.027	18.103	69.8419	3	3	3	0	2	0	12
22.209	4.212	81.0347	3	1	1	1	2	0	
46.315	33.073	28.5912	3	2	3	0	2	0	5
96.63	92.74	4.02566	5	5	2	0	4	1	0
14.94	3.27	78.1124	2	1	1	1	4	0	
8.294	4.536	45.3099	4	2	2	0	4	1	0
15.456	9.777	36.743	3	4	4	0	2	0	3
37.08	11.782	68.2255	3	1	2	0	2	0	
29.71	9.087	69.4143	3	2	4	0	2	0	3
121.72	84.794	30.3368	5	5	3	0	2	0	2
58.1	54.879	5.54389	5	5	4	0	4	1	1
50.112	18.123	63.835	4	3	4	0	2	0	20
15.752	0.723	95.4101	1	1	3	0	2	0	12
41.244	4.5	89.0893	3	2	3	0	2	0	8
40.56	4.937	87.8279	3	1	3	0	2	1	0
			4		2	0	4	0	
46.2	18.8	59.3074	4	2	4	0	2	0	2

Data sheet: page 1-continued

293908F	M	74	1	2	2	1	3	1	T4bN2M0	8	1
290225F	M	52	3	2	3	0	1	3	T3N1M0	7	1
300302F	M	23	1	1	7	1	1	1	T3N0M0	3	1
298293F	F	36	1	2	3	1	1	1	T3N2aM0	7	1
303406F	F	66	1	1	34	1	1	1	T3N2M0	7	1
313633F	M	57	1	1	6	1	1	1	T3N2M0	7	1
326007F	M	55	1	1	9	1	1	2	T3N2M1a	9	1
330519F	M	66	1	2	7	0	1	1	T3N2M0	7	0
357883F	M	67	1	2	2	0	1	3	T3N0M0	3	0
270382F	M	56	1	1	6	1	1	1	T3N2M1b	10	1
381232F	F	60	1	2	4	1	3	1	T3N1M0	7	1
369780F	M	60	1	2	5	1	1	1	T3N2M0	7	1
368898F	F	63	1	1	5	1	2	1	T4bN2M0	8	1
334484F	M	49	1	1	6	1	1	1	T4bN2M0	8	1
362032F	F	40	2	2	30	1	2	1	T3N2M1b	10	1
363342F	M	63	1	2	5	1	2	1	T3N1M0	7	0
396172F	M	28	1	2	7	1	2	3	T3N2bM0	8	1
247777F	M	33	1	2	7	1	3	3	T3N2M0	7	1
368817F	F	47	1	1	10	1	1	1	T3N1M0	7	1
405673F	M	51	1	2	7	1	1	1	T3N2M0	7	1
405742F	F	62	1	2	7	1	2	1	T3N2M0	7	0
377076F	M	39	1	1	7	1	1	2	T4bN2M0	8	1
404378F	M	69	1	1	3	1	1	2	T4N1M0	8	1
431536F	M	56	1	1	7	1	1	1	T3N1M0	7	1
318204F	M	51	1	1	11	1	1	2	T3N1M0	7	1
355793F	M	45	1	1	3	1	1	1	T3N2M1a	9	1

Data sheet: page 2-continued

T4N2M0	8	1	0	0.691	0.875	184	79.627	60.415	24.12749
T3N0M0	3	0	1.5	0.876	1.7475	871.5	31.17	0	100
T2N1Mx	6	1	0	0.883	1.366	483	10.28	1.6	84.4358
T3N1Mx	7	0	4	0.781	1.096	315	41.22	3.306	91.97962
T3N1M0	7	1	0	0.845	1.187	342	12.9	12.05	6.589147
T3N1Mx	7	1	0	0.845	1.904	1059	10.238	2	80.46493
T3N0Mx	3	1	0	0.836	1.073	237	31.307	9.958	68.19242
T3N0Mx	3	0	4	0.932	1.498	566	16.12	1.5	90.69479
T3N0Mx	3	0	9	1.088	1.443	355	9.053	0.017	99.81222
T3N1M1	10	1	0	0.942	1.669	727	20.775	5.194	74.9988
T3N0M0	3	0	3	0.855	1.0907	235.7	19.105	8.415	55.95394
T3N1M1b	10	1	0	0.903	1.289	386	6.059	1.338	77.91715
T4bN1M0	8	1	0	0.754	1.014	260	49.07	2.7	94.49766
T3N0M0	3	1	0	0.698	1.501	803	28.66	0.288	98.99512
T3N2M1b	10	1	0	0.758	0.7575	-0.5	58.572	5.07	91.34399
T2N1M0	6	0	3	1.077	1.359	282	13.32	0	100
T3N2M0	7	1	0	0.973	1.027	54	30.725	5.53	82.00163
T3N2M0	7	1	0	1.325	1.42	95	41.03	0.114	99.72215
T3N0M0	3	0	5	0.794	1.294	500	20.77	1.72	91.71883
T3N1M0	7	1	0	0.643	1.284	641			
T3N0M0	3	0	7	0.772	1.384	612	14.07	0.63	95.52239
T4N2M0	8	1	0	2.102	2.312	210	77.93	63.56	18.43963
T4N0M0	5	1	0	1.36	1.518	158	64.47	8.63	86.61393
T2N0M0	2	0	3.4	0.818	1.394	576	16.978	0.81	95.22912
T3N1M0	7	1	0	2.02	2.043	23	101.695	87.511	13.94759
T3N0M0	3	0	4	0.817	1.374	557	53.946	0.247	99.54213

Data sheet: page 3-continued

134.432	55.202	58.9369	4	4	4	0	2	1	1
30.74	7	77.2284	2	3	1	1	6	0	
18.28	4.94	72.9759	4	4	3	0	2	1	1
52.02	6.402	87.6932	3	3	3	0	2	0	8
17.182	15.624	9.06763	4	2	4	0	2	0	2
22.7	6.56	71.1013	3	1	3	0	2	0	6
62.36	43.34	30.5003	4	3	3	0	2	0	4
16	0	100	2	1	4	0	2	0	9
7.778	7.65	1.64567	3	2	1	1	2	0	
35.1	14.617	58.3561	4	3	3	0	2	0	2
12.615	6.454	48.8387	3	2	4	0	2	0	2
17.95	8.63	51.922	2	1	2	0	2	1	1
79.42	25.441	67.9665	2	2	4	0	3	1	0
30.88	6.016	80.5181	3	2	1	1	7	0	
41.365	4.83	88.3235	3	3	3	0	2	0	7
11.88	3.965	66.6246	2	1	1	1	2	0	
25.905	4.988	80.745	4	2	5	0	5	1	0
31.218	17.595	43.6383	4	4	2	1	4	0	8
16.79	6.432	61.6915	3	3	2	1	2	0	
			3		1	1	2	0	
10.493	2.41	77.0323	2	1	2	0	2	0	20
79.44	72.56	8.66062	5	5	2	0	2	1	0
74.02	44.37	40.0567	4	3	2	0	4	1	0
14.203	0.738	94.8039	2	1	2	0	2	0	6
118.08	98.665	16.4422	4	4	4	0	3	1	0
60.714	4.65	92.3411	2	2	1	1	2	0	